Archives of Internal Medicine

VOLUME 51 MARCH, 1933 NUMBER 3

CATAPHORETIC VELOCITY OF STREPTOCOCCI AS ISOLATED IN STUDIES OF ARTHRITIS

EDWARD C. ROSENOW, M.D.

ROCHESTER, MINN.

One of the reasons why the importance of streptococci in the etiology of rheumatic fever and various other forms of arthritis, especially chronic infectious arthritis, is not sufficiently recognized is the fact that bacteriologists have been too much concerned with differences in cultural reactions and not enough with the peculiar infecting power of the streptococci isolated, especially immediately after isolation. The diseases comprising the arthritic group, generally considered as being due to streptococci, are so different in their clinical and pathologic manifestations, and the cultural properties of streptococci are so variable,[1] that the requirements stressed by some [2] that all streptococci isolated must have identical cultural reactions to be of significance is fallacious. In a long series of experiments, I have shown that the streptococci isolated in cases of rheumatic fever [3] and chronic infectious arthritis,[4] irrespective of whether they are green-producing, indifferent or slightly hemolytic, possess on isolation peculiar localizing and disease-producing powers. The conditions at hand in the patients from whom the various types were isolated were often closely simulated in inoculated animals. The three types of streptococci (green-producing, slightly hemolytic and indifferent) which I isolated from tonsils, blood, joints,

From the Division of Experimental Bacteriology, the Mayo Foundation.

1. Rosenow, E. C.: Transmutations Within the Streptococcus-Pneumococcus Group, J. Infect. Dis. **14**:1 (Jan.) 1914. Todd, E. W.: The Conversion of Hemolytic Streptococci to Non-Hemolytic Forms, J. Exper. Med. **48**:493 (Oct.) 1928.

2. Birkhaug, K. E.: Rheumatic Fever. Bacteriologic Studies of a Non-Methemoglobin-Forming Streptococcus with Special Reference to Its Soluble Toxin Production, J. Infect. Dis. **40**:549, 1927. Clawson, B. J.: Studies on the Etiology of Acute Rheumatic Fever, ibid. **36**:444, 1925. Small, J. C.: The Bacterium Causing Rheumatic Fever and a Preliminary Account of the Therapeutic Action of Its Specific Antiserum, Am. J. M. Sc. **173**:101 (Jan.) 1927. Swift, H. F.; Derick, C. L., and Hitchcock, C. H.: Rheumatic Fever as a Manifestation of Hypersensitiveness (Allergy or Hyperergy) to Streptococci, Tr. A. Am. Physicians **43**:192, 1928.

3. Rosenow, E. C.: The Etiology of Acute Rheumatism, Articular and Muscular, J. Infect. Dis. **14**:61 (Jan.) 1914.

4. Rosenow, E. C.: Etiology of Arthritis Deformans, Preliminary Note, J. A. M. A. **62**:1146 (April 11) 1914.

muscles and regional lymph nodes in cases of rheumatic fever [5] (isolated since from the blood in a high percentage of cases of Cecil, Nicholls and Stainsby [6]), besides having marked affinity for joints (66 per cent of 71 animals inoculated), had marked affinity for the heart (in 46 per cent endocarditis developed; in 44 per cent, myocarditis). Similar strains, isolated from atria of infection, excised tissues and regional lymph nodes draining arthritic joints in cases of chronic infectious arthritis [7] also had marked affinity for joints (53 per cent of 1,447 animals given injections) but little affinity for the heart (in only 5.5 per cent of animals given injections did lesions of the cardiac valves develop, and less than 1 per cent had lesions of the myocardium).

Indeed, the method of intravenous injection of the streptococcus as obtained from various atria of infection and the making of cultures from the tissue affected has served to separate the saprophytes from the pathogens and has served to isolate the probable causative streptococcus in a long series of cases of chronic infectious arthritis and other diseases.[7a] Serologic studies with hyperimmune serums prepared in the horse from representative strains of streptococci isolated in studies of chronic infectious arthritis have shown that most of the strains thus isolated are immunologically alike.[8] Agglutination with the serum of the patient, however, was not sufficiently striking to be of constant diagnostic significance.[8] The method of intravenous injection of freshly isolated organisms, too, has its limitations. It is costly, time-consuming and difficult, and is not always successful. Some investigators [9] have had difficulty in corroborating my results. To prove a causal relationship of streptococci in studies of chronic infectious arthritis by making cultures of fluid from the joints is impossible, because cultures are nearly always negative.[4] The method of making cultures from excised articular tissues and regional lymph nodes, although more often positive,[10] is painful and impracticable on a large scale. Cutaneous tests for hypersensitiveness, attempts at desensitization with antigens prepared from streptococci, relief from symptoms following removal of

5. Rosenow, E. C.: The Newer Bacteriology of Various Infections as Determined by Special Methods, J. A. M. A. **63**:903 (Sept. 12) 1914.

6. Cecil, R. L.; Nicholls, Edith E., and Stainsby, W. J.: Bacteriology of the Blood and Joints in Rheumatic Fever, J. Exper. Med. **50**:617 (Nov.) 1929.

7. Rosenow, E. C.: (*a*) Focal Infection and Elective Localization, Internat. Clin. **2**:29 (June) 1930; (*b*) footnotes 4 and 5.

8. Rosenow, E. C.: Serologic Specificity of Streptococci Having Elective Localizing Power as Isolated in Various Diseases of Man, J. Infect. Dis. **45**:331, 1929.

9. Valentine, Eugenia, and Van Meter, Martha: The Localization of Streptococci in the Tissues of Rabbits, J. Infect. Dis. **47**:56, 1930.

10. Margolis, H. M., and Dorsey, Anna H. E.: Chronic Arthritis; Bacteriology of Affected Tissues, Arch. Int. Med. **46**:121 (July) 1930. Rosenow (footnotes 4 and 5.)

foci of infection and the use of vaccines prepared from streptococci that have been shown to have elective localizing power, although of great value in some cases,[11] cannot solve the problem of etiology. Isolation of streptococci from the blood, so successfully accomplished by Cecil, Nicholls and Stainsby,[12] and corroborated by me in several groups of cases but not in others,[10] although of great value if the results are positive, also has its limitations. The successful agglutination experiments conducted by these workers with the serum of patients and the production of arthritis in animals with their typical strains are the most consistent proof yet produced of etiologic relationship, but here too there are disturbing factors. Their strains are hemolytic and extremely sensitive to agglutination, and the streptococci which we and others [13] have isolated in studies of chronic infectious arthritis and myositis are chiefly green-producing or indifferent and usually resist agglutination by the serum of the patient.[8] The need for further study of the problem by new methods, especially for identification of the streptococci and proof of their etiologic relationship in acute and chronic infectious arthritis and in "rheumatic" arthritis, is apparent.

In a preliminary report, Jensen and I [14] have shown that streptococci having elective localizing power, as isolated from atria of infection in studies of encephalitis and arthritis, have characteristic cataphoretic velocity, and that the respective serums have specific potential lowering effects on these streptococci. It is my purpose in this report to describe the technic and to record results obtained in a further study of streptococci isolated in cases of arthritis.

11. Rosenow, E. C., and Nickel, A. C.: Results in Various Diseases from Elimination of Foci of Infection and Use of Vaccine Prepared from Streptococci Having Elective Localizing Power, J. Lab. & Clin. Med. **14**:504 (March) 1929.

12. Cecil, R. L.; Nicholls, Edith E., and Stainsby, W. J.: The Bacteriology of the Blood and Joints in Chronic Infectious Arthritis, Arch. Int. Med. **43**:571 (May) 1929; footnote 6.

13. Haden, R. L.: The Elective Localization of Bacteria in Peptic Ulcer, Arch. Int. Med. **35**:457 (April) 1925. Meisser, J. G., and Brock, Sam: A Clinical and Experimental Study in Chronic Arthritis, J. Am. Dent. A. **10**:1100 (Dec.) 1923. Moench, L. Mary: The Relationship of Chronic Endocervicitis to Focal Infection with Special Reference to Chronic Arthritis, J. Lab. & Clin. Med. **9**:289 (Feb.) 1924. Nakamura, T.: A Study on Focal Infection and Elective Localization in Ulcer of the Stomach and in Arthritis, Ann. Surg. **79**:29 (Jan.) 1924. Nickel, A. C.: The Localization in Animals of Bacteria Isolated from Foci of Infection, J. A. M. A. **87**:1117 (Oct. 2) 1926. Rosenow (footnotes 4, 5 and 7). Rosenow, E. C., and Ashby, Winifred: Focal Infection and Elective Localization in the Etiology of Myositis, Arch. Int. Med. **28**:274 (Sept.) 1921. Valentine and Van Meter (footnote 9).

14. Rosenow, E. C., and Jensen, L. B.: Elective Localization and Cataphoretic Potential of Streptococci. Preliminary Report, Proc. Soc. Exper. Biol. & Med. **27**:442, 1930.

METHOD OF STUDY

The method of obtaining material for cultures, and the preparation of cultures for study of cataphoretic velocity and inoculation of animals, were essentially like those used in work on elective localization. The materials from the nasopharynx, tonsils, pyorrheal pockets about the teeth, prostate gland or uterine cervix and fluid and tissue from joints were plated as a routine on blood-agar and used for inoculation of tall columns of previously warmed dextrose-brain broth. Material from the apexes of pulpless teeth was used for inoculation of tall columns of dextrose-brain agar in addition, because the streptococci from these regions are anaerobic and will not grow on blood-agar plates in primary culture. Cultures from the stool were made by plating on blood-agar plates in series, and single colonies of streptococci were fished and used for inoculation of the test medium, dextrose-brain broth, for studies of cataphoretic velocity. The cultures were incubated at 35° C. for from eighteen to twenty-four hours, rarely longer. If the growth on the primary blood-agar plates revealed a preponderance of colonies of streptococci, and if the culture in brain broth had grown with diffuse turbidity, without formation of gas, which was the rule, about 2 cc. was poured into scrupulously clean test tubes. This amount was centrifugated just sufficiently to clear the broth. The supernatant fluid was then thoroughly drained off, and the sediment was suspended as evenly as possible in 12 cc. of distilled water, and this, after it had stood for a short time to allow bubbles of gas to escape, was poured into a Northrop-Kunitz-Mudd cataphoresis apparatus. It was found that when the growth on the primary blood-agar plate revealed a great preponderance of colonies of streptococci, and the culture in dextrose-brain broth had grown with diffuse turbidity, and without formation of gas, film preparations and platings of dextrose-brain broth always revealed pure or nearly pure cultures of streptococci that grew in short chains. Hence, these methods of verification, although used in each new disease studied until the characteristic type of velocity had been established, were omitted in routine work. If the primary blood-agar plate revealed a preponderance of staphylococci, which occurred sometimes in work with nasopharyngeal swabbings, but almost never in work with cultures from apexes of pulpless teeth and never in cultures from affected joints of animals that had received injections, or if the plates revealed bacilli and the dextrose-brain broth culture grew with formation of gas, film preparations and platings were always made to verify the studies of cataphoresis. However, even if the plates revealed bacilli and the dextrose-brain broth culture grew with formation of gas, a great preponderance of streptococci having characteristic velocities was the rule. The determinations of velocity were made at approximately constant voltage (120 volts) and temperature (20 to 24 C.), and a stop watch was used to note the time required for each of from ten to twenty organisms, depending on the evenness of their rate of migration, to traverse 50 microns, the unit distance. The time required in seconds and fourths of seconds for each organism to traverse this unit distance was recorded, and from this the cataphoretic velocity was determined in terms of microns per second, per volt per centimeter, according to the formula:

$$\text{Cataphoretic velocity} = \frac{50 \text{ microns}}{\text{time in seconds} \times \text{potential gradient (7.8 volts per cm.)}}$$

For example, most streptococci derived from patients with chronic infectious arthritis traverse the unit distance of 50 microns in the cataphoretic cell in three seconds, and the effective potential gradient as the cell was used was found to be 7.8 volts per centimeter by actual measurement; hence, microns per second, per volt per centimeter, equals $\frac{50}{3 \times 7.8}$, or 2.13.

TABLE 1.—*Cataphoretic Velocity of Streptococci as Isolated in Studies on Arthritis*

Diseases	Source of Streptococcus	Strains: Number	Strains: Per Cent: Neurotrope	Arthrotrope	Normal	Rhinotrope	Pharyngotrope	Bronchotrope	Other	Cultures: Number	Cultures: Per Cent: Neurotrope	Arthrotrope	Normal	Rhinotrope	Pharyngotrope	Bronchotrope	Other	Streptococci Timed: Number	Streptococci Timed: Per Cent: Neurotrope	Arthrotrope	Other
Chronic infectious arthritis: cultures from nasopharynx, tonsils, teeth, prostate gland or uterine cervix	A*	189	5	70	10	3	4	2	6	329	11	64	12	2	5	5	1	4,082	19	60	21
	J*	31	0	87	10	0	0	3	0	66	2	83	7	2	4	2	0	600	15	65	20
Chronic infectious arthritis: cultures from teeth, not included in larger series	A	39	13	63	16	0	0	0	0	75	11	73	11	0	1	4	0	1,009	25	58	17
	J	8	0	88	12	0	0	0	0	19	0	89	11	0	0	0	0	214	21	59	20
Acute infectious arthritis: cultures from nasopharynx	A	11	0	100	0	0	0	0	0	13	0	100	0	0	0	0	0	211	10	76	14
	J	3	0	100	0	0	0	0	0	5	0	100	0	0	0	0	0	85	6	63	31
Arthritis: old cultures after long cultivation on artificial mediums	J	16	0	69	25	6	0	0	0	17	0	65	29	6	0	0	0	231	23	56	21
Neuromyositis with or without arthritis: cultures from nasopharynx, tonsils or teeth	A	10	50	40	0	0	0	10	0	48	52	46	0	0	0	2	0	502	50	30	20
	J	2	50	50	0	0	0	0	0	18	39	50	0	0	0	11	0	335	40	39	21
Epidemic encephalitis: cultures from nasopharynx, tonsils, teeth, prostate gland or uterine cervix	A	55	96	0	4	0	0	0	0	96	96	1	3	0	0	0	0	1,418	65	12	23
	B*	15	93	0	7	0	0	0	0	34	94	0	6	0	0	0	0	528	57	16	27
Tuberculosis of bones and joints: cultures from nasopharynx	A	14	0	14	64	8	14	0	0	14	0	14	64	8	14	0	0	135	22	47	31
Normal persons: cultures from nasopharynx	A	345	1	11	76	3	4	1	3	345	1	11	76	3	4	1	3	3,574	25	46	29

* A = atrium of infection of patient; J = joints of animals that had been given injections; B = brains of animals that had been given injections.

The operator in most instances was unaware of the diagnosis in the cases in which the culture or cultures were obtained. Cultures of material from atria of infection of patients having different diseases, and from old cultures, were purposely included on the same day in order to be sure that the results were reliable.

In table 1 and in the text, cultures containing a preponderance of streptococci with a velocity of 2.29, 2.13 or 2 microns per second, per volt per centimenter, are designated as arthrotropic because streptococci of these velocities occur in great preponderance in cases of arthritis. Those with a velocity of 3.56, 3.2 or 2.91 and those with velocities of 1.68, 1.6 or 1.52 microns per second, per volt per centimeter, are designated as poliomyelitic or neurotropic because these velocities

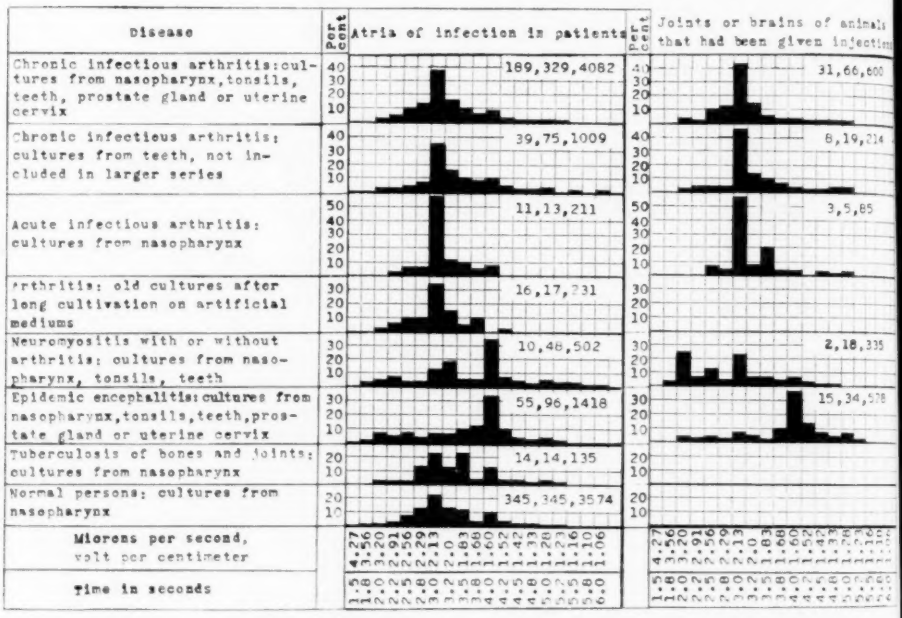

Fig. 1.—Cataphoretic velocity of streptococci as isolated in studies of arthritis. The numbers inserted in the right upper corner of each graph indicate, respectively, the number of strains, cultures and streptococci timed in each group studied.

predominate in poliomyelitis, encephalitis and other diseases of the nervous system. Those with a distribution of velocities like those of streptococci from throats of normal human beings in times free from epidemics, in which there is a moderate preponderance of streptococci having a velocity of 2.29, 2.13 or 2 microns per second, per volt per centimeter, are designated as normal. Those with a velocity of about 2.56 microns per second, per volt per centimeter, are designated as rhinotropic, because this is the predominating velocity of streptococci isolated from the nasopharynx in cases of acute rhinitis. Those with a velocity of about 1.83 microns per second, per volt per centimeter, are designated as pharyngotropic, because this

is the predominating velocity of streptococci isolated from the nasopharynx in cases of pharyngitis or sore throat. Those with a velocity of chiefly 1.83, 1.6, 1.42 or 1.28 microns per second, per volt per centimeter, are designated as bronchotropic, because streptococci with such velocities are commonly at hand in cases of influenza, affecting chiefly the throat and bronchi, and associated with marked constitutional reactions.

The number of streptococci the velocity of which was determined in individual strains and cultures was approximately the same in the different groups. The percentage incidence of the different velocities, as shown in figures 1 and 2, was determined by dividing the number of streptococci that had these different velocities by the total number of streptococci timed in each group.

In the course of previous studies, specific agglutination was sometimes obtained with the serum of the patient, the streptococci isolated in studies of the disease

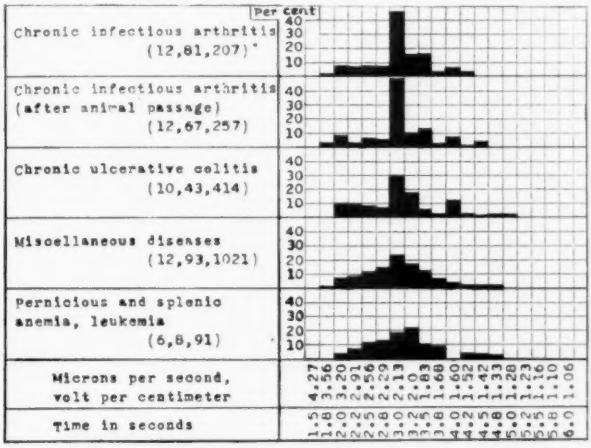
Per cent
Chronic infectious arthritis (12,81,207)*
Chronic infectious arthritis (after animal passage) (12,67,257)
Chronic ulcerative colitis (10,43,414)
Miscellaneous diseases (12,93,1021)
Pernicious and splenic anemia, leukemia (6,8,91)
40
30
20
10
Microns per second, volt per centimeter
4.27 3.56 3.20 2.91 2.56 2.29 2.13 2.03 1.83 1.68 1.60 1.52 1.42 1.33 1.28 1.23 1.16 1.10 1.06
Time in seconds
1.5 1.8 2.0 2.5 2.8 3.0 3.5 3.8 4.0 4.5 4.8 5.0 5.5 5.8 6.0

Fig. 2.—Cataphoretic velocity of streptococci as isolated from the stool in cases of chronic infectious arthritis and other diseases. The figures in parenthesis indicate, respectively, the number of strains, cultures and streptococci timed in each group studied.

with which the patient was suffering being used; the streptococci were agglutinated in high dilution in the corresponding hyperimmune horse serums, but the agglutination in serum from patients was not constant enough to be of unmistakable diagnostic value. It occurred to me that possibly the serum of the patient might lower specifically the cataphoretic velocity of the streptococcus in question in sufficiently high dilution for the evidence thus obtained to be of unquestioned value. Accordingly, a series of experiments was undertaken to determine the most reliable method by varying the density of the suspensions, the electrolyte content, the duration and degree of heating of the suspensions and the method of holding constant the characteristic potential of stock suspensions of the different strains of streptococci. The following technic was adopted as most reliable, and the results recorded in table 2 were obtained by its careful application.

Dilutions of serum were made as a routine, in series, in suspensions of bacteria as follows: 1 to 20, 1 to 40, 1 to 80, 1 to 160, 1 to 320, 1 to 640, 1 to 1,280 and 1 to 2,560, and sometimes also 1 to 5,120 and 1 to 10,240, each tube containing 1.5 cc. The diluted suspensions of the respective streptococci were made from stock, dense suspensions (1,000,000,000,000 streptococci in each cubic centimeter) in glycerin (2 parts), and 25 per cent sodium chloride solution (1 part), which had been kept in the refrigerator. The dense suspensions were diluted with distilled water to about a fourth the density of dextrose-brain broth cultures, or

TABLE 2.—*Specific Velocity-Slowing Effect of the Serum from Patients with Arthritis on Streptococci Isolated in Studies of Arthritis*

Serums	Streptococcal Suspensions		
	Arthritis	Encephalitis	Poliomyelitis
Chronic infectious arthritis (2)*	1:1280†	1:80	1:80
Chronic infectious arthritis (3)	1:2560	1:80	1:80
Chronic infectious arthritis (2)	1:5120	1:640	
Chronic infectious arthritis (2)	1:1280	1:320	
Chronic hypertrophic arthritis (2)	1:1280	1:80	1:40
Subacute infectious arthritis	1:640	1:80	1:80
Acute arthritis	1:2560	1:40	1:80
Rheumatic arthritis (2)	1:1280	1:160	1:160
Chronic spondylitis	1:640	1:80	1:40
Chronic arthritis and myositis	1:1280	1:80	1:80
Periarthritis	1:2560	1:40	1:80
Neuromyositis and arthritis (2)	1:1280	1:640	1:320
Neuromyositis (2)	1:1280	1:320	1:80
Neuromyositis	1:640	1:80	1:40
Chronic parkinsonian encephalitis (2)	1:80	1:2560	1:80
Recurring encephalitis	1:80	1:2560	1:40
Chronic parkinsonian encephalitis	1:80	1:640	1:320
Mild chronic encephalitis	1:80	1:1280	1:40
Acute myoclonic encephalitis	1:80	1:320	1:40
Acute myoclonic encephalitis (2)	1:80	1:1280	1:40
Acute parkinsonian encephalitis	1:80	1:5120	1:2560
Acute poliomyelitis (3)	1:40	1:40	1:1280
Acute poliomyelitis	1:160	1:320	1:5120
Acute poliomyelitis	1:160	1:160	1:2560
Convalescent poliomyelitis (2)	1:80	1:80	1:2560
Convalescent poliomyelitis (2)	1:80	1:40	1:1280
Convalescent poliomyelitis	1:160	1:320	1:5120
Normal serum (2)	1:40	1:20	1:80
Normal serum (5)	1:80	1:80	1:80
Normal serum (2)	1:80	1:40	1:40
Normal serum (3)	1:40	1:40	1:40
Normal serum (2)	1:80	1:80	1:40
Normal serum (3)	1:160	1:160	1:160
Normal serum (2)	1:80	1:80	1:320
Normal serum	1:320	1:320	1:640
Normal serum	1:160	1:320	1:320

* Figures in parenthesis indicate number of cases.
† The highest dilution in which the serum had a velocity-slowing effect.

about 500,000,000 streptococci in each cubic centimeter. If more dilute suspensions in glycerin and salt solution were used, requiring the addition of a larger quantity of sodium chloride, or electrolyte, the suspension in water was washed once and resuspended in water. After the suspensions and serum had been thoroughly mixed, the set-up was placed first in the incubator for one hour and a half, in the oven at 52 C. for two hours and then in the refrigerator over night. The following morning the tubes were inspected for evidence of macroscopic agglutination, the controls consisting of suspensions only, and each mixture, containing various amounts of serum, in turn was diluted with 14 cc. of distilled water and was poured into the cataphoretic cell, and the rate of migration was determined in the usual manner.

RESULTS

The results obtained from a study of cataphoretic velocity of the streptococci isolated from atria of infection in the different groups of cases and controls are summarized in table 1, and shown graphically in figure 1, and those isolated from the stool are shown in figure 2. The high incidence is noteworthy, in strains and cultures, of a preponderance of streptococci having arthrotropic velocity, as isolated from various atria of infection in cases of chronic infectious arthritis (63 to 100 per cent), especially after animal passage (87 to 100 per cent); a similar high incidence was noted in cases of acute infectious arthritis. These results are in sharp contrast to the almost complete absence of arthrotropic strains as isolated from atria of infection in studies of cases of epidemic encephalitis; it is also in contrast to a very low incidence of arthrotropic organisms (11 to 14 per cent) in the strains and cultures isolated from the nasopharynx in patients with tuberculosis of the bones and joints and in normal persons. After the arthritic strains had been cultured on artificial mediums for a long time they lost much of the arthrotropic velocity, and the configuration of the curve resembled closely that of streptococci from the throats of normal persons. Most interesting of all, the strains and cultures before and after animal passage, from atria of infection in the group of cases of neuromyositis, with or without arthritis, were partly neurotropic and partly arthrotropic.

The percentage incidence in the different groups of all streptococci that had arthrotropic and neurotropic velocities was in close agreement with that of the percentage incidence of strains and cultures having streptococci chiefly of these velocities. The total distribution of velocities in each of the groups studied is shown graphically in figure 1. The consistently high incidence of streptococci having arthrotropic velocity, highest in cultures made from atria of infection in acute cases of arthritis and from the joints of animals that had received injections, is well shown and is in sharp contrast with the graphs illustrating the velocity of streptococci isolated in studies of cases of encephalitis. The velocities of the streptococci isolated in cases of neuromyositis occupy an intermediate position between the velocities of streptococci isolated in studies of arthritis and those from encephalitis. The seeming discrepancy between the figures illustrating the velocities of the strains before and after animal passage in the neuromyositis group is really not a discrepancy, because the neurotropic streptococci which traverse the unit distance of 50 microns in four seconds before animal passage commonly traverse it twice as fast after animal passage, and on cultivation of these strains on artificial mediums they often revert in speed by a multiple of 2. The similarity of the distribution of velocities of the arthritic strains, especially after long cultivation on artificial mediums,

and of those isolated from the nasopharynx in normal persons and in persons having tuberculosis of the bones and joints is also well shown.

The distribution of cataphoretic velocity of all streptococci timed from single colony cultures of the stool on blood-agar as subsequently grown in dextrose-brain broth is represented graphically in figure 2. The incidence of arthrotropic velocity of the streptococci isolated in cases of chronic infectious arthritis, before and after animal passage, is extremely high. The distribution of velocities is practically normal in single colony cultures of streptococci derived from the stool in cases of chronic ulcerative colitis, miscellaneous diseases taken together, pernicious anemia, splenic anemia and leukemia. Most of the streptococci found in suspensions, made directly in distilled water, of nasopharyngeal swabbings and in pus from tonsils in cases of arthritis had arthrotropic velocity.

The serum in cases of arthritis has been found to have far greater effect in slowing the rate of migration (reduction of electric charge) of streptococci obtained in studies of arthritis than in slowing the velocity of streptococci isolated in cases of encephalitis and poliomyelitis, and in much higher dilution. In the lower dilutions of serum the streptococci isolated in cases of arthritis were rendered isopotential. In table 2 are summarized the results obtained with the serum from persons having different forms of arthritis and neuromyositis with and without arthritis, in contrast with the serum from persons having encephalitis or poliomyelitis and with that from normal persons. The suspensions of streptococci isolated in cases of arthritis, used mainly in these experiments, consisted of ten strains of green-producing streptococci isolated from the affected joints of rabbits following intravenous injection of the streptococci from various atria of infection in cases of chronic infectious arthritis. The suspensions of streptococci from persons with encephalitis and poliomyelitis were isolated either from the nasopharynx, and were used after one animal passage, or were isolated from the brain and cord of patients with encephalitis and poliomyelitis. There were twenty-four strains in the encephalitis suspension and nine strains in the poliomyelitis suspension. All three suspensions represented the growth from 0.2 per cent dextrose broth which had been preserved in very dense suspension in glycerin (2 parts) and 25 per cent sodium chloride solution (1 part) for from one to ten years. It will be noted that the serum in cases of various forms of arthritis had a slowing effect in far higher dilution on the arthritic streptococci than on the streptococci obtained in cases of encephalitis or poliomyelitis. The results of agglutination in low dilution, when positive, agreed with velocity-slowing effects, but in these experiments, as heretofore, such agglutination occurred too irregularly to be of undoubted diagnostic value. The serum in cases of neuromyositis affected most markedly,

and in high dilution, the streptococci with arthrotropic velocity from patients with arthritis, but affected also, moderately, the streptococci from patients with encephalitis which had neurotropic velocity. The results of serum potential studies proved helpful in differential diagnosis in several cases belonging in the group of neuromyositis, in which, from clinical manifestation and roentgenograms, it was impossible to say whether the pain over the distribution of the sciatic nerve (sciatica) was due to arthritis, to sacro-iliac subluxation or to neuritis. The presence in the nasopharynx of a great preponderance of streptococci having arthrotropic velocity and a particularly marked slowing effect of the serum on arthrotropic streptococci were considered to indicate arthritis; a great preponderance of streptococci having neurotropic velocity and a marked slowing effect on neurotropic streptococci, as indicating neuritis; a combination of these velocities and serum effects, as indicating both arthritis and neuritis, and a normal nasopharyngeal streptococcal flora and normal velocity-reducing effect, as indicating merely mechanical impingement on the nerve roots. The serum of patients with encephalitis affected markedly, and in high dilution, the streptococci isolated in cases of encephalitis, but the effect of this serum on the streptococci from patients with arthritis, and with two exceptions its effect on the streptococci from patients with poliomyelitis, were no greater than that of normal serum. The serum from patients with poliomyelitis and from persons having recovered from poliomyelitis affected most markedly, and in high dilution, the streptococci of poliomyelitis, but this serum affected, scarcely more than normal serum, streptococci from patients with encephalitis and arthritis. These specific effects are in sharp contrast to the somewhat variable but always relatively slight effect on each of the respective strains of the serum from normal persons. Results comparable to these were obtained with autogenous strains of streptococci isolated in cases of arthritis with other heterologous strains and with heated and unheated suspensions, both as isolated and after preservation in the glycerin-salt solution menstruum. It made little difference whether the strains were green-producing (which was usually the case), indifferent, slightly hemolytic or markedly hemolytic on blood-agar plates. The velocity of almost all strains was specifically reduced by the serums of patients with arthritis, provided the cataphoretic velocity or potential was arthrotropic; if the strains were not arthrotropic, the serum of patients with arthritis had no more, or only a slightly greater, effect than serum from normal persons.

Absorption experiments with the arthrotropic streptococci removed specifically from the serum of patients with arthritis its power of reducing velocity. In a number of cases the titer of serum increased markedly as patients recovered from relatively acute attacks of arthritis.

In addition to the striking evidence, as shown in table 1 and figures 1 and 2, of the importance of determination of the arthrotropic potential or velocity in learning the capabilities of localization in joints of streptococci isolated from patients with arthritis, it has been found that when cultures containing a mixture of streptococci, having respectively arthrotropic and neurotropic velocities, are injected, a pure or almost pure culture of streptococci having arthrotropic velocity is obtained from the joints, and a pure or almost pure culture of streptococci having neurotropic velocity is obtained from the brain. This occurred in cultures obtained from a joint and the brain or from a joint or the brain of nine rabbits which had received intravenous injections of seven strains containing streptococci having neurotropic velocity. It also occurred with three other strains containing streptococci of different velocities injected intraperitoneally into one mouse and intravenously into one rabbit. The cultures from the brains of these animals were often positive, even when there were no symptoms of encephalitis during life; the cultures from the brains of normal rabbits were never positive.

A markedly arthrotropic streptococcal flora was found in the nasopharynx of each of six patients suffering from supposedly senescent arthritis. Moderately positive serum potentials against arthrotropic streptococci were demonstrated in each of three of these cases. In each of three cases of active chronic infectious arthritis, and in two of neuromyositis, the characteristic abnormal cataphoretic velocity of streptococci, as isolated from the nasopharynx, became normal coincidentally with marked improvement and the prolonged use of vaccines prepared from strains that had specific localizing power and characteristic cataphoretic velocity. The serum of each of these patients developed a marked cataphoretic velocity-slowing effect on the respective streptococci. With the return of symptoms following discontinuance of administration of the vaccine, the streptococcal flora of the nasopharynx, having chiefly arthrotropic velocity, again returned. The streptococci isolated in the usual manner from the nasopharynx and other foci of infection in each of nine cases of acute rheumatic arthritis had mainly arthrotropic velocity.

The usual high incidence of elective localization and marked lesions in joints was noted in this new series of experiments as in all series previously studied in which cultures were made from patients with arthritis. Thus, in 64 per cent of one hundred and six rabbits that were given injections of sixty-four strains isolated from patients with arthritis, arthritis developed; in 21 per cent lesions developed in the muscles, in 8 per cent in the endocardium, and in 6 per cent in the myocardium. Lesions of nerves did not develop in any. In 71 per cent of seven rabbits that were given injections of one or another of four strains

isolated from patients with "rheumatic" arthritis, arthritis developed; in 43 per cent, myositis developed, in 29 per cent, endocarditis, and in 29 per cent, myocarditis. In none did lesions of the nerves develop. In 37 per cent of thirty-five rabbits that were given injections of one or another of eight strains derived from persons suffering from neuromyositis, arthritis developed; in 66 per cent, myositis; in 11 per cent, endocarditis; in 11 per cent, myocarditis, and in 46 per cent, lesions of the nerves. These results are in sharp contrast with those following the injection of strains obtained in a similar manner from normal persons and from persons (control group) ill with diseases other than the arthritic group. In experiments with strains representing the control group, in only 21 per cent of eighty-seven rabbits that were given injections of one or another of forty-three strains did arthritis develop; in 8 per cent, myositis developed; in 3 per cent, endocarditis; in 6 per cent myocarditis, and in 1 per cent, lesions of the nerves. The lesions of the joints in the present series of experiments were usually more marked and more joints were involved, as in former studies, in the animals receiving injections of organisms derived from patients with arthritis than in the animals which received injections of organisms from the control group. The power of the streptococcus obtained in cases of arthritis to produce arthritis was roughly proportional to the acuteness of the attack suffered by the patient from whom the organisms were isolated and to the number of streptococci that had arthrotropic velocity in the culture. As indicated, the strains obtained in the cases of "rheumatic" arthritis associated with involvement of the heart, in this series of experiments as in the former series, had, in addition to marked affinity for the joints, marked affinity for the heart, especially for the heart valves and myocardium, whereas those isolated in cases of chronic infectious arthritis without involvement of the heart had marked affinity for joints and slight affinity for the heart. The cataphoretic velocity of the two groups of strains was about the same, although individual organisms having neurotropic velocity were more common in the cultures from the cases of rheumatic arthritis. There was little difference in the cataphoretic velocity, and indeed in the localizing power, of the streptococci as isolated from the various atria of infection in individual cases of arthritis, although it sometimes happened that the velocity of streptococci in cultures from one of several foci in an individual case was atypical. It was common in cases of neuromyositis, when more than one focus was cultured, that arthrotropic velocities predominated in one and neurotropic velocities in others.

In the strains from patients suffering from myositis, with or without arthritis, associated with a variable degree of neuritis, comprising the neuromyositis group, the affinity for joints, muscles and nerves

corresponded closely with the affected regions of the patients from whom the organisms were isolated; also, the organisms had chiefly the corresponding characteristic cataphoretic velocity or potential. The strains isolated from lesions in muscles of inoculated animals remote from nerves and from joints contained a preponderance of streptococci having arthrotropic velocity, and those isolated from the affected nerves remote from lesions in muscles had chiefly neurotropic velocity. However, nearly all of these cultures from lesions that were produced in animals contained a mixture of streptococci having chiefly arthrotropic and neurotropic velocities (fig. 1), as did the strains isolated from atria of infection of patients. The results in one case of severe, incapacitating, acute neuromyositis, radiculitis and arthritis were especially striking. The cataphoretic velocity of the streptococcus as isolated on two occasions a week apart, from the nasopharynx and infected pockets surrounding teeth, was typical in all cultures tested. Of eight rabbits given intravenous injections, arthritis developed in seven, lesions of the muscles in seven, chiefly along nerves and blood vessels, and hemorrhagic lesions in nerves and nerve sheaths in seven. In addition to symptoms of pain in this patient there were marked nervousness and nervous exhaustion, which persisted for weeks, but following removal of the infected teeth there was gradual recovery. Concomitant with the marked involvement of the central nervous system, the streptococcus penetrated the central nervous system following intravenous inoculation of four rabbits, producing meningo-encephalitis and radiculitis.

Blood-agar platings of cultures from infected teeth of patients and of turbid fluid from affected joints of animals that had been given injections were nearly always sterile when cultures in dextrose-brain broth or in dextrose-brain agar revealed pure cultures of streptococci that grew in short chains, and that had chiefly arthrotropic velocity. Cultures of turbid fluid from the joints, even in dextrose-brain broth and dextrose-brain agar, sometimes remained sterile. Especially was this so in cultures from animals that had been given injections a considerable time previously. By the making of cultures from excised pieces of bone and other tissues, positive results were obtained more often, but even under these circumstances growth sometimes remained absent. Smears of fluid from the joints sometimes revealed undoubted diplococci when cultures remained sterile, and sometimes growth of streptococci occurred when no organisms could be found on direct examination of stained films. It occurred to me that perhaps the reaction in the joints might be due to a filtrable virus, or that the streptococcus might have become filtrable and difficult to grow. Accordingly, filtrates were made of emulsions of tissues of involved joints, of negative cultures of fluid from the joints in dextrose-brain broth, of negative cul-

tures of emulsions of tissue and of positive cultures of streptococci in this medium. All cultures from filtrates of tissues that had remained sterile, from filtrates of fluid from the joints and from sterile cultures of these remained sterile, whereas filtrates of some of the positive streptococcic cultures in dextrose-brain broth from atria of infection and from joints revealed pure cultures of streptococci having chiefly arthrotropic velocity and corresponding elective localizing power. Intravenous and intra-articular injection of negative cultures and filtrates negative on culture have never caused arthritis, whereas similar injection of corresponding filtrates of positive cultures have yielded mild "toxic" lesions. Cultures from joints showing these lesions were always sterile, and direct transfers of exudates thus obtained to joints of other rabbits failed to produce arthritis.

Staphylococci were frequently isolated, but nearly always in small numbers and never in pure cultures, from apexes of teeth and from the joints of rabbits that had been given intravenous injections of primary cultures in dextrose-brain broth, even in instances in which platings of the culture injected revealed colonies of staphylococci. Pure cultures of staphylococci, obtained only rarely in the primary culture in dextrose-brain broth, and those fished from single colonies of cultures from the various foci of infection and joints of animals that were given injections of cultures of streptococci in which a small number of staphylococci were present, nearly always revealed mixed velocity, and never a preponderance of organisms having arthrotropic velocity. The serum of patients with chronic infectious arthritis in no instance had a greater velocity-slowing effect on the staphylococci isolated than had normal serum, indicating that these staphylococci were not etiologic.[15]

As has been shown previously, freshly isolated cultures from atria of infection, such as the nasopharynx of normal persons and of persons ill with diseases other than arthritis, sometimes produce arthritis in animals following intravenous injection, but the arthritis is usually mild in degree, and the incidence is far lower than that following injection of cultures from patients with arthritis. On the basis of studies of cataphoresis this should be so, for streptococci having arthrotropic velocity are uniformly present in considerable numbers in the nasopharynx of normal persons and sometimes of persons ill with diseases other than arthritis. The cataphoretic velocity of the streptococci obtained from the joints of animals in which arthritis had developed following injection of cultures derived from normal persons and from persons ill with diseases other than arthritis was chiefly arthrotropic.

15. Crowe, H. W.: Bacteriology and Surgery of Chronic Arthritis and Rheumatism with End-Results of Treatment, New York, Oxford University Press, 1927.

In one group of normal persons, swabbings were repeatedly made before, during and after an epidemic of influenza, and marked variation in cataphoretic velocity of streptococci from the nasopharynx was noted with changes in season. The velocity of the streptococci cultured from the sets of swabbings made during the epidemic resembled that of the streptococci obtained in cases of influenza. In the cultures made from swabbings soon after the epidemic of influenza had disappeared, the velocity of the streptococci became markedly arthrotropic, and one person who had a particularly great preponderance of streptococci of arthrotropic velocity had an attack of arthritis shortly thereafter. Coincidental with this, and with a high incidence of arthrotropic velocity of streptococci in cultures from the nasopharynx as patients recovered from influenza, there was a noticeable increase in the number of cases of arthritis. The streptococcic strains from patients with influenza, after culture on blood-agar, acquired arthrotropic velocity and marked affinity for joints. Three months after the epidemic of influenza had disappeared, the cataphoretic velocity of the streptococci from the nasopharynx of the group of normal persons, swabbed repeatedly, had again become characteristic of the velocity of streptococci derived from normal persons in nonepidemic times. Details of these experiments will be published elsewhere.

In addition, considerable variation in the percentage incidence of streptococci having arthrotropic velocities has been found, the incidence sometimes approaching that obtained in cases of chronic infectious arthritis and in different groups of normal persons, particularly in groups swabbed in different localities and institutions at different seasons. Arthrotropic velocity and elective localizing power were particularly high in streptococci isolated from persons who had arthritis, and who were resident at an institution where an epidemic of acute arthritis was occurring; the epidemic was traced to a Streptococcus lacticus starter used in preparing cottage cheese from pasteurized milk. It might well be that the abnormally high incidence of arthritis in rabbits given injections of cultures from normal persons reported by Valentine and Van Meter [9] may have been due to incidental causes such as these. Moreover, cataphoretic studies have been of great value in explaining the reason for unusual localizations in certain instances, such as were noted by these investigators in their relatively small number of experiments and by me throughout many years of effort in work on elective localization. Most of these puzzling irregularities, considered by Valentine and Van Meter [9] as explainable by the law of chance, have been found to be due to sudden dissociation of strains as determined by cataphoresis. The changeability or mutability of streptococci is basic to the concept of elective localization; indeed, the theory had its origin in

the work on transmutation of pneumococci and streptococci. The isolation of streptococci having chiefly arthrotropic velocity from various atria of infection in cases of arthritis in the absence of influenza has been almost constant over a period of several years, and on repeated occasions over a period of many months, in some cases of progressive chronic arthritis. Likewise, the streptococci from atria of infection of persons having chronic encephalitis and allied diseases of the nervous system have been found to have chiefly neurotropic velocity. However, with the appearance of an epidemic of influenza, the streptococcic flora of the nasopharynx of normal persons generally within the epidemic zone, and of persons suffering from arthritis, encephalitis and other diseases, became influenzal, and, most remarkable of all, the respective characteristic streptococci isolated in nonepidemic times with great regularity from the apexes of pulpless teeth of persons having arthritis or encephalitis and other diseases became influenzal, irrespective as to whether the patients had had influenza or not. This peculiar condition of the streptococcus from teeth persisted for several months and disappeared as the streptococcic flora of the nasopharynx again became normal in normal persons, and characteristic of the disease in question in patients presumably suffering from disease due to streptococci.

Drs. R. L. Cecil, E. E. Nicholls and W. J. Stainsby [12] have given me the opportunity of studying three of their typical strains of streptococci isolated from the blood in cases of chronic infectious arthritis. All produced marked hemolysis on blood-agar plates, and all grew well in dextrose-brain broth, but produced a slightly granular growth instead of a diffuse growth as do the strains of streptococci which I isolate. However, most of the streptococci in cultures in dextrose-brain broth and on blood-agar plates had arthrotropic velocity through a series of rapidly transferred cultures. All produced marked arthritis in rabbits following intravenous injection in a dosage like that used with my strains, and from the joints pure cultures of hemolytic streptococci were isolated. The streptococci in the cultures from all but one joint had mainly arthrotropic velocity, whereas those of one joint had acquired a velocity closely resembling that of the streptococci derived from patients with influenza. This culture was injected intraperitoneally into two rats, both of which died with characteristic lesions of the pancreas, lung and pleura, and the strain isolated from the pleural exudate had influenzal velocity. These experiments were done at the time of an epidemic of influenza in Rochester. A similar dissociation of some of my strains, isolated in cases of arthritis, occurred in rabbits that had received injections during the epidemic of influenza, but such dissociation never occurred in the course of many similar experiments during the absence of epidemic influenza.

COMMENT

The distribution of the different velocities of streptococci as isolated from atria of infection and from the stools of normal persons in which arthrotropic velocity is dominant seems to be a "resting phase" of streptococci, for the different strains having characteristic velocity, as isolated in studies of various diseases, tend, in nonepidemic times, to take on this distribution during prolonged cultivation on artificial mediums. Velocity of this distribution is displayed by streptococci on isolation from the nasopharynx of persons ill with diseases due to causes other than streptococci, such as tuberculosis of the joints, and on isolation from the stools of normal persons and of patients with diseases not apparently due to streptococci (fig. 1). This is likewise true of streptococci isolated in nonepidemic times from the milk of cows and from other dairy products. This distribution of different velocities is considered of basic importance, for it suggests, perhaps, that the great frequency of arthritis may be due in part to this cause.

During an epidemic of influenza, in addition to persons ill with influenza, a large proportion of normal persons and those ill with other diseases, such as arthritis and encephalitis, became carriers of the streptococcus having influenzal velocity. Following the epidemic, however, the streptococcal flora in each group again became characteristic: That of normal persons became normal, that of persons with arthritis became arthrotropic and that of persons with encephalitis became neurotropic. These and other facts indicate that dissociation or mutation of streptococci plays an important part in the etiology of various forms of arthritis and allied conditions, and of epidemic disease generally.

It has been shown in this and previous studies that persons having different diseases, for example chronic arthritis, are more or less permanent carriers of streptococci characteristic of arthritis, in that the streptococci possess an abnormally high elective affinity for joints, and in that a great preponderance have arthrotropic velocity. The fluids from the tissues of the patients seem to afford conditions favorable for streptococci to acquire these particular properties. On the basis of these observations, as I have previously suggested, it would seem that the inherited tendency to arthritis, or "rheumatic" diathesis, mentioned by the older writers, is more than the inheritance of weak joints, as is usually assumed. There is an inheritance of weak joints, plus, perhaps, a peculiar constitution or chemical make-up, which is favorable for streptococci present normally in atria of infection, or during epidemics of influenza, to acquire a peculiar arthrotropic cataphoretic velocity and infecting power.

CONCLUSIONS

Streptococci isolated from patients who have arthritis, in the absence of epidemic influenza, have a characteristic arthrotropic cataphoretic velocity and at the same time an elective localizing power, irrespective of whether the organisms are green-producing, indifferent or hemolytic on blood-agar.

The serum of patients having various forms of arthritis has specific cataphoretic velocity-slowing effects on the streptococcus isolated in cases of arthritis, and that is shown to have arthrotropic velocity. An arthrotropic cataphoretic velocity of the streptococcus as isolated and a specific slowing effect of the patients' serum on arthrotropic streptococci have been found to be almost constant phenomena. The method of determining cataphoretic velocity has yielded results of etiologic importance, and has proved of great value in the control of the specificity and dosage of autogenous and heterologous streptococcus vaccines used in treatment. If this method is properly applied, it is no longer necessary to inject cultures from atria of infection intravenously into animals and to make cultures from their joints in order to be certain that the streptococcus isolated is etiologic or has characteristic infecting and antigenic power. Determination of the cataphoretic velocity usually suffices.

BRONCHIAL DISINFECTION AND IMMUNIZATION

I. THE EFFECTS IN RABBITS OF INTRABRONCHIAL INJECTIONS OF VARIOUS CHEMICAL DISINFECTANTS

JOHN A. KOLMER, M.D.
PHILADELPHIA

The frequency of the chronic intractable bronchitides, extensive bronchiectasia and other nontuberculous suppurative infections of the bronchi and lungs commonly grouped under the designation of suppurative pneumonitis, along with the well established fact that ordinary medicinal treatment possesses little or no real value, renders this relatively large group of pulmonary infections worthy of further investigation in relation to both etiology and treatment. This is particularly true since bronchiectasis not unfrequently begins in childhood and sometimes results in semi-invalidism for many years and indeed for the balance of life.

Fortunately, bronchoscopic drainage and bronchial lavage have definitely improved the treatment and prognosis of bronchiectasis and these allied conditions. Bronchoscopic drainage, as developed by the brilliant investigations of Jackson, Tucker, Clerf and others, has at least largely aided in the treatment in those cases due to foreign bodies [1] and, along with bronchography, has greatly improved methods of diagnosis as well as provided a means for removing collections of purulent secretions and making direct or topical applications of medicinal agents. Unfortunately, however, the bronchoscope cannot reach the smaller bronchi, and it may not be practical to make direct applications of bactericidal agents through it with the frequency that is demanded. For these reasons the possibilities of bronchial lavage as developed by Stitt [2] and others, as well as the intubation method recently described by Iglauer [3] for the introduction of iodized oil for bronchography in chil-

---

From the Research Institute of Cutaneous Medicine and the Laboratories of the Graduate School of Medicine of the University of Pennsylvania.

Aided by a grant from the Faculty Research Committee of the Board of Graduate Education and Research of the University of Pennsylvania.

1. Jackson, C.: Suppurative Diseases of the Lung Due to Inspirated Foreign Body Contrasted with Those of Other Etiology, Surg., Gynec. & Obst. **42**:305, 1926.

2. Stitt, H. L.: Bronchial Aspiration and Irrigation with a Hypertonic Saline Solution, J. Med. **8**:112, 1927.

3. Iglauer, S.: Advantages of Intubation Method of Introducing Iodized Oil for Bronchography in Children, J. A. M. A. **97**:1517 (Nov. 21) 1931.

dren, commands considerable interest. In other words, any method that permits the frequent, even the daily removal of bronchial secretions and the instillation of bactericidal and bacteriostatic agents with the minimum of discomfort and danger is to be welcomed as opening up a possible means for improving the treatment of these distressing infections.

Certainly the ease and success attending bronchography in adults and children with instillations of iodized oil indicate that the pulmonary tissues may tolerate relatively large amounts of bland solutions capable of reaching the infected finer divisions of the bronchi beyond the reach of direct applications through the bronchoscope; hence, the possibility of improving the treatment of bronchiectasis and allied conditions by the local application of chemotherapeutic substances as well as with such biologic agents as vaccines, bacteriophages and antiviruses is established.

ETIOLOGY

While it is not within the scope of this communication to discuss in detail prevailing views and personal investigations bearing on the etiology of the untractable bronchitides and bronchiectasia, a brief reference to the subject is necessary in relation to these studies undertaken in regard to intrabronchial disinfection and immunization.

Aside from those cases due to probable congenital deficiencies in the bronchi and foreign bodies, it is my opinion that the majority are due to bacterial infection and especially to streptococci and staphylococci. At least this is the impression gained during the past six years as the result of bacteriologic examinations of a large number of specimens collected by bronchoscopy and submitted for examination by Dr. Chevalier Jackson and Dr. Gabriel Tucker.

In my experience, streptococcic infections are by all odds the most frequent and important and appear to be the prevailing infection in both early and late cases of purulent bronchitis and bronchiectasis. Indeed, they have not infrequently been present in pure cultures, and considering the fact that they have been collected under conditions greatly minimizing or entirely removing the chances of contamination with saliva with reasonable certainty, I have the conviction at present that they bear an important etiologic relationship to these infections. Staphylococci, pneumococci, various gram-negative diplococci, including M. catarrhalis, diphtheroid bacilli, B. pyocyaneous and B. friedländer, are also encountered in chronic infections as would be expected, but streptococci, staphylococci and pneumococci would appear to be the more important in relation to the primary infection.

Spirochetes are sometimes seen in direct smears and more especially by dark-field examination, but not in my experience with the

frequency suggested by Smith [4] and others. In view of the numerous species to be found in the saliva and gingival secretions, especially in adults, it is to be expected that they may reach the bronchi in chronic infections and constitute secondary infection. However, it is possible, in some cases at least, that they may possess the etiologic importance assigned to them by Smith in producing primary infection of the bronchial walls and favoring the development of pockets analogous to the rôle of Spirochaeta pallida in the production of aneurysms, but I hesitate accepting this view in individual cases unless relatively large numbers are found in the secretions or until microscopic examination of tissues removed at autopsy more definitely establish this relationship. Furthermore, it would appear that Spirochaeta vincentii and B. fusiformis may produce a type of Vincent's infection of the pulmonary tissues, but in the large majority of the chronic bronchitides and bronchiectasia my findings assign a more frequent and important rôle to the bacteria with special reference to the streptococci.

Various molds and yeasts are sometimes recovered in cultures of secretions from chronic bronchial infections, but so far these have been almost entirely of the various Aspergilli and Penicillia commonly found in the dusts of the house and factory. It is to be expected that molds of these and other species may have some bearing on the production of allergic asthma, but with the exception of such pathogenic species as Actinomyces their rôle and importance as etiologic agents in suppurative pneumonitis are as yet to be determined.

PRINCIPLES OF CHEMOTHERAPY APPLIED TO BRONCHIAL DISINFECTION

While sanatorium regimen, frequent postural drainage, elimination of mouth and sinus infection, bronchoscopic removal of foreign bodies and secretions and various surgical procedures are logical measures of value in the treatment of suppurative pneumonitis, as recently emphasized by Alexander and Buckingham,[5] yet it would appear that the possibilities of local disinfection by chemotherapeutic agents, applied bronchoscopy or bronchial lavage are worthy of serious attention.

However, but little has been done so far in this direction. Castex, Heidenreich and Repetto [6] have reported favorably on intrabronchial

4. Smith, D. T.: Relation of Vincent's Angina to Fusospirochetal Disease of the Lungs, J. A. M. A. **94**:23 (Jan. 4) 1930. Gives a good review of earlier literature.

5. Alexander, J., and Buckingham, W. W.: Treatment of Nontuberculous Suppurative Pneumonitis, Abscess and Bronchiectasis, J. A. M. A. **95**:1478 (Nov. 15) 1930.

6. Castex, M. R.; Heidenreich, A. J., and Repetto, R. L.: Le salvarsan par voie trachéale dans le traitement des Processes fétides de l'appareil respiratoire, Bull. Acad. de méd., Paris **95**:131 (Feb. 9) 1926.

injections of neoarsphenamine in the treatment of spirochetic infections, and Stiehm,[7] the Ballons[8] and others refer to the possible curative effects of intrabronchial injections of iodized poppy seed oil 40 per cent, although the bactericidal activity of the latter is so low that it is possible that the benefit observed was due to other factors. Gomenol has been applied by Jackson, Tucker and others through the bronchoscope with apparently some benefit, which is to be expected, since this oil possesses some bactericidal activity, as I shall discuss later, but otherwise no systematic attempts at local disinfection appear to have been made, although a number of antiseptics have been tried.

Naturally a relatively large list of bactericidal agents is available for the choice of compounds to be employed, but it would appear that substances selected for attempted bronchial disinfection should possess the following essential properties:

1. A reasonably high degree of parasiticidal activity in the presence of pus and especially for streptococci, staphylococci and other bacteria, spirochetes and fungi.

2. Be rapidly parasiticidal because the time of contact must be necessarily brief.

3. Preferably stain the tissues in order to prolong antiseptic or bacteriostatic action.

4. Possess the maximum degree of penetrability in order to reach and destroy micro-organisms entrenched in cells and tissues.

5. Be free of injurious effects on phagocytes in order not to interfere with phagocytosis which doubtless exerts an important rôle in the mechanism of resistance and recovery.

6. Be free of injurious effects on the pulmonary tissues. That is, the chosen antiseptic should not exert excessive hyperemia or inflammatory changes, abolish the cough reflex or interfere with ciliary action and bronchial peristalsis.

7. Be sufficiently low in toxicity to spare the kidneys, liver and other organs injurious effects following absorption from the lungs.

8. Furthermore, the solution employed for irrigating the bronchi and for preparing solutions of the chosen antiseptic should not favor the development of edema, especially since the tissues are already injured by infection. For this reason the use of calcium and potassium salts with sodium chloride in any irrigating fluid is regarded as superior to sodium chloride alone, and the following Martin-Bledsoe irrigant has been recommended:

	Gm. or Cc.	
Sodium chloride	10	5
Potassium chloride	0	42
Calcium chloride	0	84
Distilled water	1,000	0

7. Stiehm, R. H.: Treatment of Bronchiectasis with Lipoidol with Report of Nineteen Cases, Wisconsin M. J. **29**:556, 1930.

8. Ballon, R. H., and Ballon, H. C.: The Value of Bronchoscopic Injections of Lipoidol in the Diagnosis and Treatment of Bronchiectasis, J. Laryng. & Otol. **44**:153, 1929.

Stitt finds it convenient to have this solution ready in concentrated form as follows:

	Gm. or Cc.
Sodium chloride	263 | 7
Potassium chloride	10 | 6
Calcium chloride (desiccated)	21 | 0
Distilled water	1,000 | 0

For use, 20 cc. of this solution is diluted to 500 cc. with distilled or boiled water.

The solution contains, therefore, the three salts originally advocated by Ringer for maintaining the physiologic activity of surviving tissue and may be regarded as a physiologically balanced mixture. The concentration of sodium chloride has been raised somewhat above the point where it will prevent the swelling of injured cells, while the concentration of calcium chloride is several times higher to maintain the dehydrating effects of the salts as long as possible.

Since the exudates in suppurative pneumonitis are usually plastic and so rich in coagulating principles as to coagulate solid or almost so in the Tucker, Clerf or other collectors employed in bronchoscopic drainage, it would appear advisable to employ a fluid possessing liquefying or digestive properties. For this reason the alkaline antiseptics like surgical solution of chlorinated soda (Dakin's solution), command special attention, but unfortunately some chemical antiseptics are precipitated by alkalis and the pulmonary tissues greatly irritated by concentrations sufficient for liquefaction of the exudates. It may be that proteolytic enzymes may be of service in this direction, but so far my associates and I have not been able to work out a satisfactory solution of them for irrigating purposes.

But even if the foregoing requirements are fulfilled, and I believe they may be by some antiseptics, as discussed later, the important problem of adequate application to the infected tissues must be solved. This refers not only to sufficiently wide distribution in the infected areas of the lungs along with adequate drainage of the secretions, but also, and more importantly, to sufficient frequency of application.

Thus antiseptics may successfully reduce the number of pathogenic bacteria to some extent and otherwise fulfil these essential requirements, but because the bacteria escaping destruction soon begin to multiply under the favorable conditions of the lungs the original state is soon restored unless a way and means for sufficiently frequent applications is worked out.

In other words, it would appear that but little benefit may result from an occasional application of a bactericidal agent, for example, once a week, by bronchoscopic application or lavage. It would be necessary to work out a method whereby applications may be made at

more frequent intervals, even daily, for a while at least, with the minimum of discomfort and expense to the patient. For this reason I am very much interested in the possibilities of bronchial lavage, especially because it may not only afford a means of removing and washing out the purulent secretions but provide a method of instilling relatively large amounts of bacteriostatic or bactericidal solutions for reaching areas beyond direct application through the bronchoscope. In other words, it would appear that but little is to be expected from the application of antiseptics on gauze pads through the bronchoscope, because but small areas can be reached and the time of contact with the infected tissues is too brief; whereas, if it were possible to introduce and leave relatively large amounts of antiseptic solution at frequent intervals, a wider distribution and more prolonged contact may be secured with possibly greater therapeutic benefit, providing the procedure was found entirely safe and feasible.

Of course, the intravenous or intramuscular injection of chemotherapeutic agents of curative value would be the ideal treatment, but there is nothing of proved value to employ by these routes of administration except neoarsphenamine or bismarsen[9] for the treatment of Vincent's or other spirochetic infections of the lungs.

DANGERS AND CONTRAINDICATIONS TO BRONCHIAL DISINFECTION

No doubt certain dangers may attend attempts at bronchial disinfection by the direct application and instillation of antiseptics by bronchoscopy or bronchial lavage. It has already been shown by Stitt and others that 15 cc. of solution may be introduced with each inspiration. The cough reflex expels the solution along with the thick ropy secretions, so that as much as 250 cc. may be used for cleansing purposes. Under these conditions at least some of the antiseptic remains for a while in contact with the infected tissues, but my main idea was to determine if it is possible and safe to leave a portion of the last instillation for more prolonged bactericidal and bacteriostatic action without local and general injury.

The question of spreading the infection to healthy portions of the lung is important in this connection, but if bactericidal solutions are employed it would appear that this possible or theoretical danger is greatly minimized. Likewise, the danger of forcing or permitting the antiseptic solution to reach the terminal alveoli with the production of infection and pneumonitis is of importance, but I believe that it is possible to determine this danger by suitable experiments on rabbits.

9. Kolmer, J. A.: Bismuth Arsphenamine Sulphonate (Bismarsen) in the Treatment of Syphilis and of Other Spirochetic Infections, Arch. Dermat. & Syph. **21**:394 (March) 1930.

Advanced cardiovascular-renal disease, pulmonary malignant conditions and pulmonary tuberculosis may be accepted as contraindications, but it is not unreasonable to hope and expect that these methods may find a safe and useful field of application in the treatment in some cases of the latter if the results of suitable experiments on the lower animals shows that bronchial lavage and instillation of carefully selected bactericidal agents is a safe procedure.

PURPOSE OF INVESTIGATION

With these considerations in mind, the main purpose of this investigation was to select a number of the more promising bactericidal agents most nearly meeting the requirements for bronchial disinfection as outlined and determine the tolerance of the lungs of rabbits for them by repeated intrabronchial injection.

For these purposes a large number of chemical agents were tested for rapidity of bactericidal activity in the presence of protein and a number of them injected intratracheally into rabbits every two or three days in doses as high as 1 cc. per kilogram of weight of dilutions proving completely bactericidal in vitro in five minutes or less.

After from six to twenty-four instillations under ether anesthesia, the trachea, lungs and kidneys of each animal were examined macroscopically and microscopically to determine the degree of toxicity and tolerance of the tissues for each antiseptic with special reference to the bronchi. In this manner I hoped to determine whether or not it is safe not only to irrigate the lungs with bactericidal solutions but more importantly to leave relatively large amounts in the lungs without producing irritation or inflammation of the tissues. I also hoped to determine whether or not the absorption of the antiseptic from the lungs produced evidences of general toxicity with special reference to possible injury of the kidneys.

BACTERICIDAL ACTIVITY OF VARIOUS CHEMICAL AGENTS IN RELATION TO BRONCHIAL DISINFECTION

The preliminary bactericidal tests were conducted with a strain of hemolytic streptococcus and Staphylococcus aureus. While the value of these tests is limited, by conducting them in a menstrum rich in protein at body temperature the results are not without significance in the selection of compounds for intrabronchial disinfection.

The technic employed was simple, as follows: 1. To 90 cc. of sterile ascitic fluid was added 10 cc. of a twenty-four hour broth culture of the test organism, and amounts of 2 cc. were placed in sterile test tubes. 2. Solutions of each chemical compound were prepared in physiologic solution of sodium chloride and varying dilutions added in

amounts of 2 cc. each. Under these conditions the bactericidal action of each compound was determined for relatively large numbers of the organisms in a 50 per cent dilution of ascitic fluid representing a large amount of protein approximating the conditions of inflammatory exudates. 3. These mixtures were kept in a water bath at 37 C. and subcultured at the end of five minutes in order to select substances on the basis of fairly rapid bactericidal action.

The substances tested and the approximately highest dilutions completely bactericidal for the two organisms at the end of five minutes are shown in table 1.

As expected, practically all of the substances tested were more bactericidal for the streptococcus than for the staphylococcus, which is

TABLE 1.—*Bactericidal Tests*

Compound	Highest Bactericidal Dilution in Five Minutes	
	For Streptococcus Haemolyticus	For Staphylococcus Aureus
Gentian violet	1:6,000	1:4,000
Acriflavine base	1:6,000	1:3,000
Equal parts of gentian violet and acriflavine	1:6,000	1:4,000
Rivanol*	1:3,000	1:1,500
Merodicein*	1:10,000	1:5,000
Mercurochrome	1:200	1:100
Mercurophen*	1:20,000	1:15,000
Metaphen	1:60,000	1:30,000
S. T. 37 (1:1,000 hexylresorcinol)	1:3	1:2
Potassium permanganate	1:175	1:75
Mild silver protein	1:100	1:20
Gomenol*	1:60	1:8
1% iodine in 25% alcohol	1:75	1:75
Surgical solution of chlorinated soda	1:30	1:4
Chloramine T	1:600	1:400
Dichloramine T	1:300	1:75
Iodized oil	None	None
Neoarsphenamine	1:50	1:30

* Merodicein (mono-hydroxy-mercuri-di-iodo-resorcin-sulphonphthalein), mercurophen (sodium oxymercury-orthomtrophenolate), rivalol (a flavine dye) and gomenol (a preparation similar to oil of cajuput) are proprietaries and have not been accepted by the Council on Pharmacy and Chemistry of the American Medical Association.

fortunate in view of the fact that the former predominate in the secretions of purulent bronchitis and bronchiectasis.

Merodicein is of special interest, not only because it is a new compound possessing bactericidal activity but because it is a dye substance resembling mercurochrome-220 soluble in appearance, freely soluble in water and without precipitating effects on proteins and albumins. It is the disodium salt of mono-hydroxy-mercuri-di-iodo-resorcin-sulphonphthalein containing 22.78 per cent mercury, synthesized by Dunning and Farinholt.[10] Drake and Dunning[11] found it capable of killing

10. Dunning, F., and Farinholt, L. H.: J. Am. Chem. Soc. **51**:804, 1929.

11. Drake, W. E., and Dunning, F.: Organic Antiseptics: Bacteriologic Study of a New Series, J. Infect. Dis. **48**:366 (April) 1931.

B. typhosus in a dilution of about 1 : 22,500 in five minutes and Staphylococcus aureus in about 1 : 2,000. In our tests its bactericidal activity was much less because we employed large numbers of organisms and a menstruum of 50 per cent ascitic fluid representing a large amount of protein, which always reduces bactericidal activity in vitro. Macht and Cook [12] have reported that doses of from 0.010 to 0.020 Gm. per kilogram of weight by intravenous injection were generally well borne by rabbits, with but slight effect on the kidneys.

However, an objection to merodicein as a bronchial irrigant is its toxicity, evidently due in a large part to the content of mercury. The same is true of mercurochrome which was bactericidal in our tests in about a 1 per cent solution (1 : 100), although this compound is about half as toxic. Mercurophen and metaphen are at least five or six times more toxic but were likewise from ten to twenty times more bactericidal and therefore may be used for bronchial irrigation in dilutions of 1 : 5,000 or higher.

The dyes, gentian violet, acriflavine and rivanol, were bactericidal in dilutions of about 1 : 4,000, and in view of their low toxicity command great interest in relation to bronchial irrigation, particularly solutions of equal parts of gentian violet and acriflavine, since the former is especially bactericidal for gram-positive organisms, including streptococci and staphylococci, while the latter is especially bactericidal for gram-negative organisms.

While S.T. 37, or 1 : 1,000 solution of hexylresorcinol, is likewise of interest in relation to bronchial disinfection because of its low toxicity, it is unfortunately rather low in bactericidal activity and required the use of an undiluted solution (1 : 1,000), or a 1 : 2 dilution.

Mild silver protein proved of considerable interest, not only in relation to its low toxicity and staining properties but because it proved bactericidal in solutions of from 5 to 10 per cent.

Potassium permanganate was bactericidal in dilutions of from 1 : 50 to 1 : 100, and therefore commands interest as an irrigant. Iodine in the form of a 1 per cent solution in 25 per cent alcohol was especially interesting because it proved bactericidal in dilutions as high as 1 : 50 of this stock 1 per cent solution. This and its low toxicity combined with staining and penetrative properties render iodine of special interest in relation to bronchial disinfection by irrigation. Iodized oil, however, proved entirely lacking in bactericidal activity, so that whatever therapeutic properties it has been found to possess in suppurative pneumonitis must be largely due to its high specific gravity in displacing purulent secretions and promoting their expectoration.

12. Macht, D. I., and Cook, H. M.: Pharmacology and Toxicology of Monohydroxy-Mercuri-Di-Iodo-Resorcin-Sulphonphthalein, J. Pharmacol. & Exper. Therap. **43**:571, 1931.

It will be noted that gomenol, which is widely used in bronchoscopy and for irrigation of the urinary bladder, was bactericidal in dilutions of from 1:5 to 1:20, and therefore of interest in relation to bronchial disinfection.

Considerable interest attaches to surgical solution of chlorinated soda because of its dissolving effects on purulent exudates, but unfortunately it is low in bactericidal activity; dichloramine T was more bactericidal while chloramine T was bactericidal in final dilutions as high as from 1:400 to 1:600 and therefore of considerable interest in relation to bronchial disinfection, although unfortunately rather irritating to the trachea and bronchi, as discussed later.

SPIROCHETICIDAL ACTIVITY OF VARIOUS CHEMICAL AGENTS IN RELATION TO BRONCHIAL DISINFECTION

Since spirochetes are not infrequently found in the exudates of chronic bronchitis, bronchiectasis and other types of suppurative pneumonitis, it is pertinent to inquire into the spirocheticidal activity of at least some of the bactericidal agents listed in table 1 in relation to bronchial disinfection, even though the exact etiologic status of these organisms is as yet unsettled except in some instances of pulmonary spirochetosis where such enormous numbers of spirochetes are found in the profuse exudates as to leave little or no doubt of their etiologic significance.

As shown in table 1, neoarsphenamine was completely bactericidal for Streptococcus haemolyticus and Staphlococcus aureus in dilutions of about 1:50. Mixtures of equal parts of 1:25 solution and bronchial secretions containing large numbers of various spirochetes (final dilution 1:50) showed complete loss of motility within five minutes, as determined by dark-field examination. Of course, this does not necessarily imply the death of the organisms, but it is likely that under the conditions the majority at least were crippled and probably destroyed.

Additional tests with other chemical agents are shown in table 2. As a general rule, the finer spirochetes (presumably Sp. microdentium) were more easily destroyed than the larger and coarser ones like Sp. macrodentium. It was surprising, however, that the final concentrations of various agents required to cause complete loss of motility of spirochetes in purulent secretions within five minutes were many times greater than required for bactericidal activity by the method employed. For example, gentian violet, acriflavine and rivanol were spirocheticidal in from 1:100 to 1:300 but bactericidal in from 1:3,000 to 1:6,000; merodicein was bactericidal in from 1:5,000 to 1:10,000 but spirocheticidal in only 1:25; mercurophen and metaphen were bactericidal in from 1:15,000 to 1:60,000 but spirocheticidal in only 1:1,000.

Numerous experiments by Akatsu [13] have shown that neoarsphenamine and other chemical compounds are more spirocheticidal for cultures of various spirochetes than for these organisms in the secretions. For example, neoarsphenamine was spirocheticidal in vitro for cultures of Spirochaeta pallida in 1:2,500; mercuric chloride, 1:10,000, and iodine in compound solution, 1:75. Apparently, however, the presence of pus and cells in purulent secretions greatly reduce spirocheticidal activity in vitro.

But these and numerous other experiments summarized by me [14] have shown that neoarsphenamine and probably other bactericidal agents possess well defined spirocheticidal properties in vitro by local application, and it is expected that lavage of the lungs in the various types

TABLE 2.—*Spirocheticidal Tests*

Compound	Approximate Concentration Sufficient to Cause Loss of Motility in Five Minutes
Gentian violet	1:100
Acriflavine base	1:300
Rivanol	1:300
Merodicein	1:25
Mercurochrome	1:50
Mercurophen	1:1,000
Metaphen	1:1,000
S. T. 37 (1:1,000 hexylresorcinol)	Undiluted
Potassium permanganate	1:25
Mild silver protein	1:10
Gomenol	1:10
1% iodine in 25% alcohol	1:5
Chloramine T in water	1:5
Neoarsphenamine	1:50

of suppurative pneumonitis with bactericidal solutions will likewise result in the destruction of at least some of those spirochetes with which the solutions come in direct contact.

TOXICITY OF VARIOUS CHEMICAL COMPOUNDS FOR RABBITS GIVEN BY INTRABRONCHIAL INJECTION

On the completion of these bactericidal and spirocheticidal tests, I now approached the more important part of the study in relation to bronchial disinfection, namely, the toxicity of the various agents employed for rabbits when given intratracheal injections.

13. Akatsu, S.: The Resistance of Spirochetes to the Action of Hexamethylenetetramine Derivatives and Mercurial and Arsenic Compounds, J. Exper. Med. **25**:363, 1917.

14. Kolmer, J. A.: Principles and Practice of Chemotherapy with Special Reference to the Treatment of Syphilis, Philadelphia, W. B. Saunders Company, 1926, p. 342.

Preliminary experiments with iodized oil showed that the injection of 1 cc. per kilogram of weight into the trachea resulted in a widespread distribution in the bronchi as determined by roentgen examination within a few minutes after the injection (fig. 1). Sato[15] and the Ballons[8] found that injections of iodized oil into the lungs of the lower animals were well borne, and the results of our studies confirm these observations.

Normal adult rabbits were employed, and under ether anesthesia solutions of the various compounds, in a dose corresponding to 1 cc. per kilogram of weight, were injected directly into the trachea exposed by incision. As a general rule, the solutions of each compound corresponded approximately to those proving bactericidal for Staphylococcus aureus and Streptococcus haemolyticus in five minutes. It is true that the amount injected was large, since it corresponded to as much as

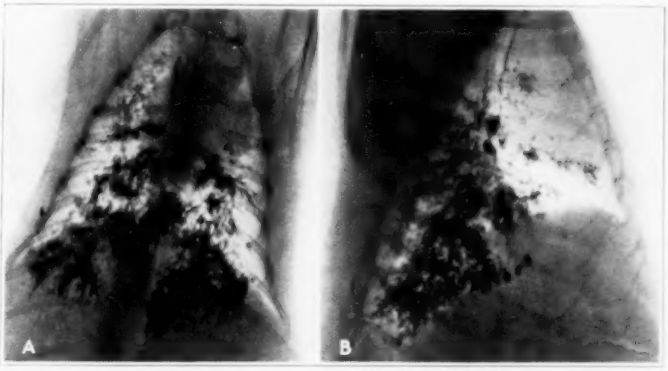

Fig. 1.—*A*, front view of the lungs of a rabbit; the roentgenogram was taken immediately after the intratracheal injection of iodized oil in dose of 1 cc. per kilogram of weight. *B*, lateral view of the lungs of the same rabbit.

60 cc. for an adult weighing approximately 135 pounds (61 Kg.), but I purposely wished to make the tests reasonably severe, even though it was realized that if chemical disinfection were to be used in the treatment of human beings probably only 15 cc. would be introduced at one time, followed by removal until about 250 cc. had been used for lavage, and only from 5 to 15 cc. would be left in the bronchi for more prolonged disinfection.

The injections were given every two days. As a general rule, several rabbits were employed for each solution and with many of the com-

15. Sato, T.: Ueber den pathologisch-histologischen Einfluss des Lipoidols und die bakterizide Wirkung desselben, Mitt. ü. allg. Path. u. path. Anat. **5**:183, 1929.

pounds solutions were tried many times stronger than their bactericidal dilutions in order to intensify the toxic effects.

On the death of the animals, or after from six to twenty-four injections had been given, autopsies were conducted with an inspection of the trachea, bronchi and lungs and sections were removed at different levels for histologic examination.

TABLE 3.—*Toxicity of Various Compounds for Rabbits by Intrapulmonary Injection*

Compounds	Dose, 1 Cc. per Kg. of:	Number of Injections	Results
Gentian violet	1:2,000	6	Survived
Acriflavine base	1:2,000	12	Survived
Equal parts of gentian violet and acriflavine	1:2,000	6	Survived
Equal parts of gentian violet and acriflavine	1:1,000	3 to 10	Died
Rivanol	1:2,000	12	Survived
Rivanol	1:1,000	10 to 17	Died
Merodicein	1:800	12	Survived
Mercurochrome	1:300	24	Survived
Mercurochrome	1:200	6 to 10	Died
Mercurophen	1:5,000	12	Survived
Mercurophen	1:1,000	5 to 7	Died
Metaphen	1:5,000	6 to 24	Survived
S. T. 37 (1:1,000 hexylresorcinol)	1:2	12	Survived
S. T. 37 (1:1,000 hexylresorcinol)	Undiluted	3 to 9	Died
Potassium permanganate	1:1,000	24	Survived
Potassium permanganate	1:500	3	Died
Mild silver protein	1:20	12	Survived
Gomenol	1:10	6	Survived
Gomenol	Undiluted	2	Died
1% iodine in 25% alcohol	1:25	12	Survived
1% iodine in 25% alcohol	Undiluted	3	Died
Surgical solution of chlorinated soda	Undiluted	6	Survived
Chloramine T in water	1:200	2	Died
Chloramine T in water	1:300	6	Survived
Dichloramine T in chlorcosane	1:20	2	Died
Dichloromine T in chlorcosane	1:200	6	Survived
Iodized oil	Undiluted	12	Survived
Neoarsphenamine	1:50	8	Survived
Martin-Bledsoe saline (control)	Control	12	Survived
Paraffin, liquid petrolatum (control)	Control	12	Survived
Olive oil (control)	Control	12	Survived
Chlorcosane solution (control)	Control	12	Survived

Table 3 presents a summary of the results so far as survival of the animals is concerned. It shows the strength of the solutions employed, the number of injections in doses of 1 cc. per kilogram every two days and whether the animals survived or succumbed. Variation in susceptibility of the animals to toxic effects was apparent; for example, three injections of a compound would sometimes result in the death of one animal, while a second would stand six injections and a third as many as twenty-four.

So far as the maximum tolerated doses of the various compounds employed are concerned, it would appear that the following represent the

approximate dilutions in doses of 1 cc. per kilogram of weight every two days for from six to twenty-four injections:

Gentian violet	1:2,000
Acriflavine base	1:2,000
Equal parts of these	1:2,000
Rivanol	1:2,000
Merodicein	1:800
Mercurochrome	1:300
Mercurophen	1:5,000
Metaphen	1:5,000
S.T. 37 (1:1,000 hexylresorcinol)	1:2
Potassium permanganate	1:1,000
Mild silver protein	1:20
Gomenol	1:10
1 per cent iodine in 25 per cent alcohol	1:25
Surgical solution of chlorinated soda	Undiluted
Chloramine T in water	1:300
Dichloramine T in chlorcosane	1:200
Iodized oil	Undiluted
Neoarsphenamine	1:50

By reference to table 1, it is observed that these maximum tolerated dilutions were bactericidal for the streptococcus and staphylococcus, with the exception of S.T. 37, potassium permanganate and iodized oil. With several, however, the maximum tolerated dilutions were but slightly higher than the bactericidal dilutions, as in the case of the dyes (gentian violet, acriflavine and rivanol), mercurochrome, mild silver protein, gomenol, surgical solution of chlorinated soda, chloramine T, dichloramine T and neoarsphenamine, whereas merodicein, mercurophen, metaphen and the iodine solution were tolerated in dilutions from three to twelve times stronger than their bactericidal dilutions. From this standpoint the last mentioned would appear to be preferred for bronchial disinfection, but a final decision on the choice of compounds was based on gross and histologic examinations for possible evidences of pulmonary irritation.

PATHOLOGIC CHANGES PRODUCED BY INTRATRACHEAL INJECTIONS OF VARIOUS COMPOUNDS

I have determined with particular care the tolerance of the trachea, bronchi and lungs of rabbits for the various disinfectants employed in this study administered by intratracheal injection, and by means of macroscopic and microscopic examination of these tissues have sought to determine their irritating properties, since it is evident that any agent chosen for bronchial disinfection should be without any pronounced

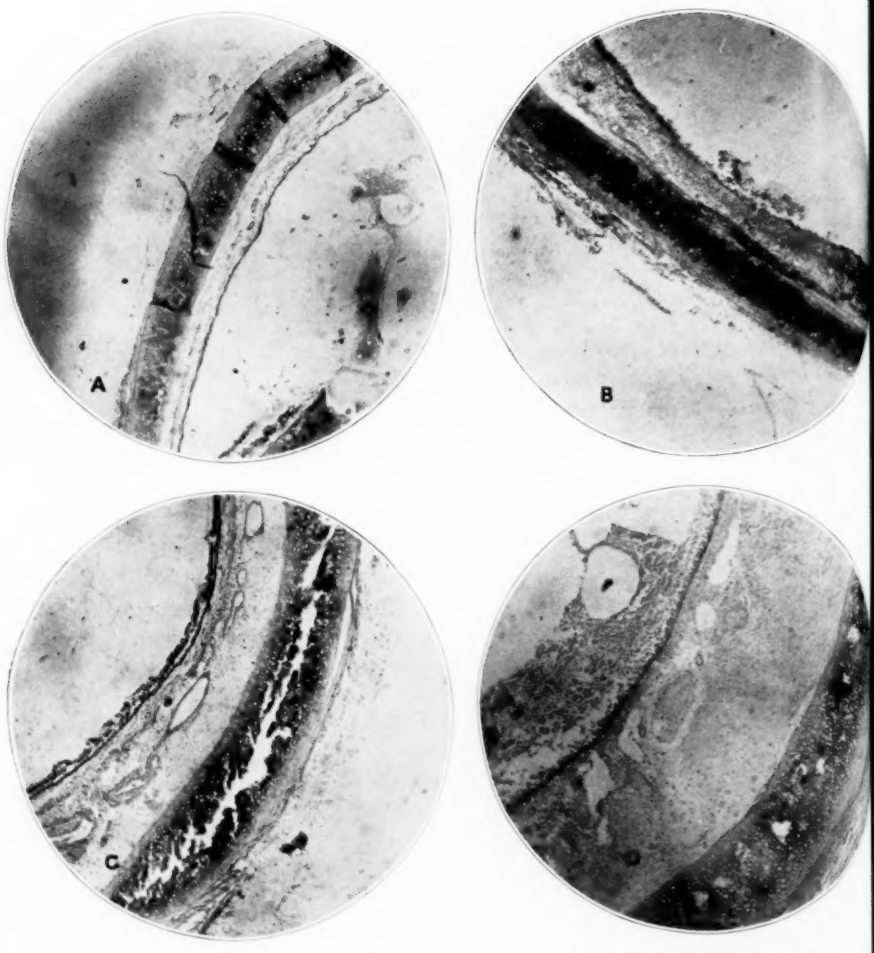

Fig. 2.—*A*, photomicrograph of a section of trachea. No changes were seen; the section was taken from the rabbit twenty-four hours after six intratracheal injections of 1:2,000 solution of acriflavine base in dose of 1 cc. per kilogram. *B*, section of trachea showing congestion, edema and hemorrhagic extravasations in the submucosa with exfoliation of the mucosa, taken from a rabbit twenty-four hours after six intratracheal injections of 1:2,000 solution of gentian violet in dose of 1 cc. per kilogram. *C*, section of trachea showing moderately severe tracheitis with extensive edema, taken from a rabbit twenty-four hours after four intratracheal injections of S.T. 37 (1:1,000) in dose of 1 cc. per kilogram. *D*, section of trachea showing very severe tracheitis with extensive congestion, edema and leukocytic infiltration with inflammatory exudate on the mucosa, taken from a rabbit twenty-four hours after six intratracheal injections of dichloramine T in water (1:100) in dose of 1 cc. per kilogram.

injurious effects. At the same time sections of the kidneys of all animals were examined for evidences of renal injury as a measure of possible systemic toxic effects resulting from the absorption of the compounds from the lungs.

For this purpose autopsies were conducted on all animals either immediately after death or twenty-four hours after the last intratracheal injection of solutions of each compound.

At least from three to six rabbits were used for each compound, and the examinations conducted after intratracheal injection of from two to twenty-four doses of 1 cc. per kilogram of weight.

Sections from the trachea were made just above the bifurcation into the primary bronchi. Sections of the lungs were selected from areas showing the maximum macroscopic changes, and sections were also made of both kidneys.

Marked variations were observed in individual animals. For example, an animal receiving three injections sometimes showed more pronounced histologic changes in the trachea, bronchi and lungs than a second animal receiving twelve injections of the same substance at the same time and in the same dosage. Furthermore, the changes produced in the lungs were more or less localized rather than diffused; as a general rule the greater changes occurred in the right lungs, especially around the primary bronchus and in the lower rather than the upper lobes. Sections were always taken from the most injured portions for histologic study.

As would be expected, the various compounds employed produced different types and degrees of injury, but I do not consider the inclusion of a detailed description of the various injuries necessary to a complete understanding of this paper; hence, in order to be as brief as possible, I have summarized them in table 4.

As expected, the bronchi have shown much more evidences of injury by all compounds than the trachea. Indeed, with but few exceptions all of the compounds employed have produced some injury of the lungs, although in this connection it should be emphasized that the doses were large and amounted to 1 cc. per kilogram every two days, corresponding to as much as from 60 to 70 cc. for an adult human being of average weight. Furthermore, it is to be remembered that all was left in the lungs after each injection rather than only a small portion. But I have purposely made the conditions very severe in order to elicit the maximum of injury.

With few exceptions all of the compounds were well borne by the trachea, although the majority produced irritation of the bronchi and

especially the smaller branches; this was particularly true in the case of those rabbits receiving from six to twenty-four injections at intervals of two days. As a general rule, these bronchial changes were of mild degree and largely in the nature of hyperemia with some edema of the submucosa, although in some instances bronchial exudates of fibrin and polymorphonuclear leukocytes were produced.

As expected, the predominant pulmonary changes were in the form of peribronchial areas of hyperemia, edema and slight leukocytic infiltra-

TABLE 4.—*Summary of Pathologic Changes in Rabbits Produced by Various Compounds by Intrapulmonary Injection**

Compound	Dilution, 1 Cc. per Kg.	No. of Doses	Trachea	Lungs	Kidneys
Gentian violet	1:1,000	3 to 10	— to ++	+ to +++	—*
Gentian violet	1:2,000	6 to 12	— to +	— to +	—
Acriflavine	1:1,000	6 to 12	— to +	— to +	—
Acriflavine	1:2,000	6 to 12	—	—	—
Rivanol	1:1,000	6 to 17	—	+ to ++	—
Rivanol	1:2,000	6 to 12	—	+ to ++	—
Merodicein	1:2,000	6 to 12	—	— to +	—
Mercurochrome	1:200	6 to 24	—	— to +++	— to +
Mercurophen	1:5,000	6 to 12	—	—	—
Metaphen	1:5,000	6 to 24	—	— to ++	—
S. T. 37 (1:1,000 hexylresorcinol)	Undiluted	3 to 9	— to +++	— to +++	— to +++
S. T. 37 (1:1,000 hexylresorcinol)	1:2	6 to 12	—	— to +	—
Potassium permanganate	1:500	3 to 9	— to +	— to ++	—
Mild silver protein	1:20	3 to 11	—	— to +	—
Gomenol	1:10	4 to 12	—	— to +	—
1% iodine in 25% alcohol	1:25	6 to 12	— to +	+ to +++	—
Surgical solution of chlorinated soda	Undiluted	3 to 8	—	+ to +++	++
Chloramine T in water	1:200	2 to 8	—	— to +	— to +
Dichloramine T in chlorcosane	1:100	2 to 8	+	+ to +++	+
Iodized oil	Undiluted	6 to 10	—	— to +	—
Neoarsphenamine	1:50	6 to 18	— to ++	— to +	— to +
Martin-Bledsoe saline solution	Control	6 to 24	—	—	—
Liquid petrolatum	Control	6 to 10	—	— to +	—
Olive oil	Control	6	—	—	—
Chlorcosane solution	Control	6	—	—	—

* The signs indicate the following: —, no demonstrable changes as applied to the trachea, (fig. 2A) bronchi and lungs (fig. 3A) or kidneys; +, slight congestion, edema and leukocytic infiltration as applied to the trachea (fig. 2B); slight peribronchial infiltration, edema and hemorrhagic extravasations as applied to the lungs (fig. 3B); acute congestion as applied to the kidneys; ++, moderately severe tracheitis with edema as applied to the trachea (fig. 2C); acute diffuse hemorrhagic pneumonitis (fig. 3C) as applied to the lungs; congestion and cloudy swelling as applied to the kidneys; +++, very severe tracheitis with extensive congestion, edema and leukocytic infiltration with inflammatory exudates (fig. 2D) as applied to the trachea; severe suppurative bronchitis and pneumonitis with abscesses and liquefaction necrosis (fig. 3D) as applied to the lungs, severe tubular or diffuse nephritis as applied to the kidneys.

tions of the alveoli. Indeed, practically all compounds produced such lesions, and especially in those animals receiving more than six injections at intervals of two days. In some instances, however, these changes were severe with relatively large areas of pneumonitis and multiple abscesses, as in the case of a large number of injections of mercurochrome, hexylresorcinol, iodine and chlorine compounds.

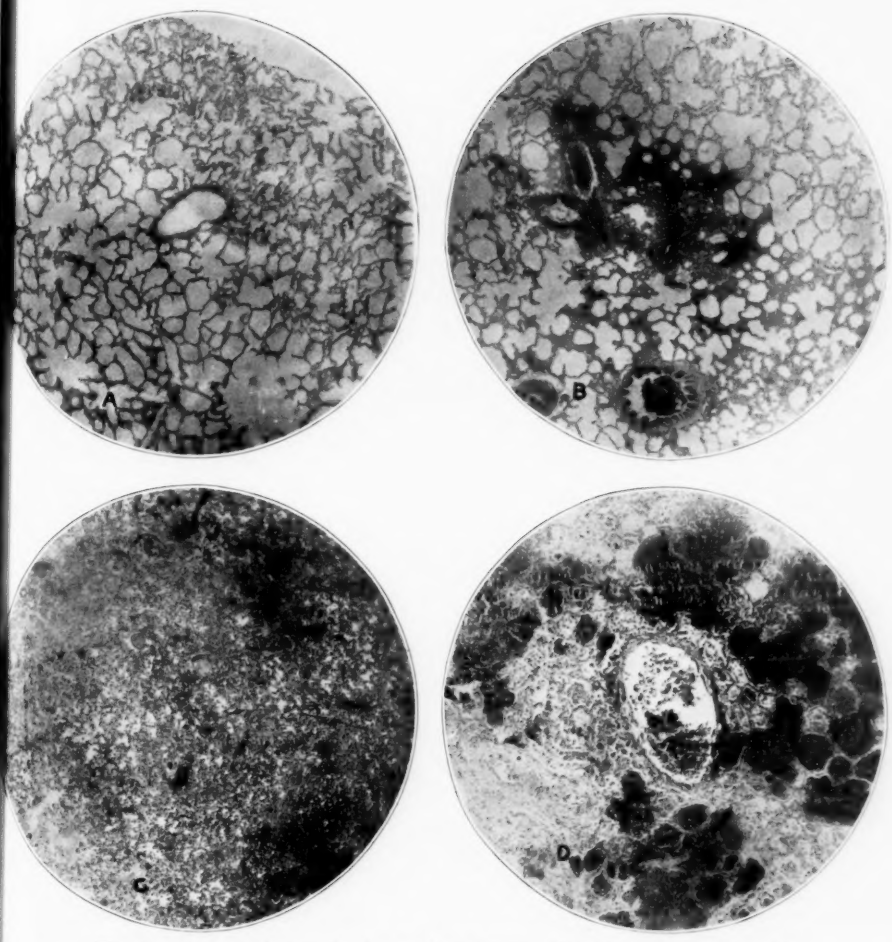

Fig. 3.—*A*, photomicrograph of a section of lung. No changes were seen; the section was taken from the lung of a rabbit twenty-four hours after four intratracheal injections of solution of acriflavine base 1:2,000 in dose of 1 cc. per kilogram. *B*, section of lung showing hemorrhagic exudate in the bronchi with slight hemorrhagic and leukocytic infiltration of the peribronchial alveolar spaces, taken from the lung of a rabbit twenty-four hours after six intratracheal injections of a 1:2,000 solution of acriflavine in dose of 1 cc. per kilogram. *C*, section of lung showing acute diffuse hemorrhagic pneumonitis, taken from the lung of a rabbit twenty-four hours after six intratracheal injections of a 1:1,000 solution of gentian violet in dose of 1 cc. per kilogram. *D*, section of lung showing very severe suppurative pneumonitis with abscesses and liquefaction necrosis, taken from the lung of a rabbit twenty-four hours after four intratracheal injections of a 1:200 solution of mercurochrome in dose of 1 cc. per kilogram.

As a general rule, there were no or but slight evidences of renal irritation, and such as were found occurred only among rabbits receiving six or more injections.

However, I believe that it is entirely likely that lavage of the bronchi of human beings with amounts of 15 cc. of the following solutions for a total of 250 cc. with the last 15 cc. left in for prolonged disinfection, would be without injurious effects at the rate of a treatment every two days or twice a week:

Gentian violet	1:2,000	
Acriflavine	1:2,000	(less irritant than gentian violet)
Merodicein	1:2,000	
Mercurophen or metaphen	1:5,000	
S.T. 37	1:2,000	(equal parts of S.T. 37 solution and saline)
Potassium permanganate	1:500 to 1:1,000	
Mild silver protein	1:20	
Gomenol	1:10	
Chloramine T	1:300	
Neoarsphenamine	1:50	

Mercurochrome 1:200 is apparently too irritating and may produce renal injury; a 1:25 dilution of a stock 1 per cent solution of iodine in 25 per cent alcohol also produced pulmonary changes, as was likewise true of surgical solution of chlorinated soda. It is to be observed that iodized oil was well tolerated in confirmation of the work of Stiehm and the Ballons, but is too low in bactericidal activity to be used for bronchial disinfection.

COMMENT AND PRACTICAL APPLICATIONS

It would appear, therefore, that bronchial disinfection may be attempted in the treatment of bronchiectasis and other types of suppurative pneumonitis by lavage with disinfectant solutions. In this connection the chosen disinfectant may be incorporated in the Bledsoe-Fisher hypertonic saline solution previously mentioned, and amounts of 15 cc. slowly passed through into the main bronchus coincident with each inspiration, followed by expulsion of the solution together with the thick ropy secretions by the cough reflex until as much as 100 to 250 cc. have been used for lavage according to the principles of the Stitt-Wooding method. Following the last lavage, I believe that it will be safe to leave 15 cc. in the bronchi for wider distribution and more prolonged bactericidal action.

Since frequency of application is undoubtedly a matter of primary importance, I hope that it will be possible to apply the treatment at daily intervals, in some instances for several days at least, followed by

subsequent treatments every two days or several times a week according to conditions. This is a matter, however, to be determined by clinical experience; all that I have hoped to show by the work summarized in this paper is that it would appear possible to employ safely a number of compounds in solutions of sufficient bactericidal activity in the presence of exudates to offer some hope of bactericidal and bacteriostatic activity along with the removal of purulent exudates by lavage as part of a program for the treatment of at least some cases of suppurative pneumonitis.

From the standpoint of choice of compound, no one has stood out predominently among those employed in this study. But it would appear that the following are worthy of trial:

(*a*) Equal parts of 1:2,000 gentian violet and 1:2,000 acriflavine.

(*b*) Mercurophen or metaphen: 1:5,000.

(*c*) Merodicein: 1:2,000.

(*d*) Equal parts of hexylresorcinol solution 1:2,000 (S.T. 37) and saline solution.

(*e*) Mild silver protein: 1:20.

(*f*) Chloramine T: 1:300.

(*g*) Neoarsphenamine: 1:100 for spirochetic infections.

Each compound may be prepared with the Bledsoe-Fisher hypertonic saline solution, and the chosen solution should be warmed to about 40 C. before administration.

According to my results, these compounds in the strengths mentioned are bactericidal in the presence of pus, do not destroy leukocytes or retard phagocytosis, appear otherwise to fulfil most of the requirements of an ideal antiseptic as previously outlined, and will probably be well borne by human beings, although the latter must be determined by clinical experience, as must the choice of the compound to be employed.

If the method is given clinical trial, the results may be judged not only by the condition and progress of the patient with special reference to the character and quantity of expectoration but by qualitative and quantitative bacteriologic examinations of the bronchial secretions. That is to say, it is readily possible to determine quantitatively with approximate accuracy the influence of treatment on the numbers of viable bacteria in the secretions by plating methods. Where spirochetes greatly predominate, it would appear possible to use intrabronchial lavage and injections of neoarsphenamine in 1:50 or 1:100 dilution and study the effects by examination of direct smears of the secretions supplemented by dark-field examinations.

SUMMARY

1. Further investigations into the etiology and treatment of the chronic bronchitides, extensive bronchiectasia and other nontuberculous suppurative infections of the bronchi and lungs would seem to be demanded because of the frequency of these conditions and the invalidism resulting therefrom.

2. Streptococci, staphylococci and other pyogenic organisms appear to be of primary etiologic importance with the possibility of spirochetes and pathogenic molds possessing primary or secondary importance in some cases.

3. The principles of chemotherapeutic disinfection by intrabronchial treatment with chemical agents are discussed; likewise, the possible dangers and contraindications to bronchial disinfection by the local or topical application of chemical agents by bronchial lavage.

4. A large number of disinfectants have been studied for bactericidal and spirocheticidal activity in vitro in a menstruum rich in protein for the selection of compounds for bronchial disinfection. Several have been found apparently suitable for this purpose.

5. Intratracheal injections of iodized oil in rabbits followed by roentgenographic examinations have shown that it is possible to secure a wide intrapulmonary distribution of solutions of chemical disinfectants by this route of administration.

6. The toxicity of a large number of chemical disinfectants has been determined in rabbits by intratracheal injections of 1 cc. per kilogram of weight every two days. The approximate maximum tolerated doses of from six to twenty-four injections are given.

7. The pathologic tissue changes produced in the trachea, bronchi, lungs and kidneys of rabbits receiving intratracheal injections of various disinfectants are presented.

8. It has been found possible to give repeated intratracheal injections of various disinfectants in bactericidal concentrations with no, or but slight, injury to the bronchi and lungs of rabbits.

9. Suggestions and a method are presented for the clinical trial of bronchial disinfection by lavage with any one of several chemical agents in the treatment of selected cases of bronchiectasis and other types of suppurative pneumonitis.

PRODUCTIVE-CICATRICIAL SYPHILITIC DISEASE OF THE PULMONARY ARTERY

HOWARD T. KARSNER, M.D.
CLEVELAND

Syphilis may affect the pulmonary artery as a productive-cicatricial lesion like that form common in the aorta, the so-called Döhle-Heller type; it may occur as a gummatous arteritis, or it may be manifested simply by the formation of gummas. Warthin further accepted as syphilitic a form of diffuse arteritis which affects principally the smaller vessels. Neither he nor Brüning, Thorel, Henschen or Rogers, all of whom he quoted in support of this view, offered definite or convincing proof. The conclusions of these investigators were arrived at by probability, exclusion or belief, based occasionally on the finding of syphilitic lesions elsewhere in the body. In spite of Peck's excellent critique of the matter, the recent report of a case by Hare and Ross is based on the presence only of suspicious lesions in the systemic aorta. These authors quoted Thomas in support of their conclusion, but many of Thomas' cases did not come to autopsy, and he reported two cases of intimal sclerosis of the pulmonary artery which he suggested were of syphilitic origin because of a history of syphilis; in one of these the Bordet-Wassermann test was twice negative and never positive! Rosenthal did not include syphilis in his theory of the pathogenesis of sclerosis of the smaller pulmonary arteries.

Peck analyzed the cases of syphilitic involvement of the pulmonary artery reported up to 1927. He accepted only twelve as definitely syphilitic. Nine of these showed either simple gumma formation or gummatous arteritis. The other three, one each reported by Barth, Henschen and Warthin, were indubitable cases of productive-cicatricial disease of the main pulmonary trunk. Peck accepted two other cases as manifestations of the extension of syphilitic lesions from the mediastinum to the pulmonary artery. The remaining fifteen cases were regarded as not proved.

A somewhat more liberal view than that of Peck would admit one of the cases that he regarded as doubtful, namely that of Ploeger. The case reported by Letulle and Jacquelin, apparently overlooked by Peck, although poorly described in the gross, was characteristic microscopically. The same may be said of one of Thomas' cases (included in his category of pure or primitive pulmonary arteritis). Since Peck's publi-

Aided by a grant from the Josiah Macy, Jr., Foundation.

From the Institute of Pathology, Western Reserve University, and University Hospitals.

cation, Plenge, who acknowledged the validity of Peck's criteria, has reported two cases of productive-cicatricial syphilitic disease of the pulmonary artery. One of Sindoni's cases may also properly be included, and the same is true of that of Reeke.[1] The case reported by Darré and Albot was not proved to be syphilitic. The present report is that of a case of unquestionable productive-cicatricial syphilitic disease of the pulmonary artery. The cases which may now be included in the group of this type of disease are shown in the accompanying table.

Cases of Productive-Cicatricial Syphilitic Disease of the Pulmonary Artery

Author	Age	Sex	Dilatation	Saccular Aneurysm	Syphilitic Aortitis
Henschen	42	F	+	?	—
Barth	57	M	—	+	—
Ploeger	52	F	+	+	+
Warthin	37	M	—	+	+
Letulle and Jacquelin	58	M	+	—	—
Thomas	38	M	—	—	?
Sindoni	42	F	+	—	+
Reeke	58	F	—	—	+
Plenge	28	F	+	—	—
Plenge	40	M	+	—	+
Karsner	28	F	+	—	+

Peck drew attention to the fact that among the twelve cases that he accepted as definitely syphilitic, nine were of gummatous type and three of productive-cicatricial type, a reversal of the proportions in aortic syphilis. If the cases in the table be accepted, the instances of both types of disease in the pulmonary artery are about equal. Even this interpretation would still leave the proportion of gummatous lesions of the pulmonary artery far higher than that of gummatous lesions of the aorta. The three cases accepted by Peck showed saccular aneurysm. The case of Reeke and the two cases of Plenge would be accepted under the strictest criteria, and these three cases were not accompanied by saccular aneurysm formation. In all instances, however, some form of definite dilatation of the artery was observed. In one of Plenge's cases the inner layers of the pulmonary artery were destroyed, and there was a dissecting aneurysm which had ruptured into the pleura.

Six of the eleven patients were women. Four were in the sixth decade, two in the fifth, three in the fourth and two in the third. The ages were from 28 to 58 years, with two cases at each of these extremes. Five patients were 40 years old or less, and six patients were more than 40 years old.

CLINICAL ABSTRACT

History.—The patient, a mulatto woman, married, 28 years old, was admitted twice to Lakeside Hospital in the service of Dr. Joseph T. Wearn. Her father and mother were dead, of unknown cause. One sister died of "pneumonia" at 22

1. Von Glahn has the protocol of an unpublished case in the records of the Department of Pathology, Columbia University, New York.

years of age. The patient had measles, mumps and pertussis in childhood and influenza in late adolescence. She was married at 18 years of age and had three pregnancies, each of which terminated spontaneously at about two and a half months. She had not been well since her last abortion in May, 1929, when she first noticed coldness and numbness of the upper extremities. In February, 1930, she noted dizziness, shortness of breath and a sensation at the xiphoid described as a "pulling-down feeling." She had periods of nausea and vomiting and a slight cough, but neither hematemesis nor hemoptysis. She had lost about 20 pounds (9 Kg.) in the six months preceding hospitalization.

Physical examination on her first admission, on June 18, 1930, showed distention of the veins in the right side of the neck, marked pulsation of the right carotid with a to and fro murmur and slight enlargement of the cervical and axillary lymph nodes. The chest moved poorly and there was enlargement of the upper mediastinal area of dulness to the left, but the lungs were clear. The left border of the heart was just within the anterior axillary line and the right border at the right sternal margin. A systolic murmur was heard at the apex, and a soft to and fro murmur suspected over the aortic area. Neurologic and general physical examination otherwise gave no significant results.

Roentgenologic examination of the chest showed marked transverse enlargement of the heart, with an unusually high aortic knob, obliteration of the incisura and, in the first oblique view, a slight compression of the trachea. The second oblique view showed localized dilatation of the aorta in its upper portion. The fluoroscope showed marked dilatation at the root of the aorta. The arteries of the arms did not pulsate, the blood pressure was not determined, and it was considered that the aortic dilatation was probably of syphilitic origin.

The urine was not abnormal. The white blood cell count was 11,900 and 9,200, and one differential count showed no abnormalities. On one occasion the blood showed 60 per cent hemoglobin (Sahli) and 5,000,000 red cells, with numerous macrocytes, slight anisocytosis and poikilocytosis, and central pale staining. On another occasion the hemoglobin was 65 per cent. The temperature ranged generally between 37 and 38 C. (98.6 and 100.4 F.), the pulse rate between 50 and 70 and the respirations between 20 and 25 with occasional records of as high as 30 per minute. The Wassermann test was 4 plus positive. The patient was kept in bed and in a wheel chair, complained of occasional pains in the left side of the chest, was treated symptomatically, without antisyphilitic measures, and at her own request was discharged on August 17.

At her home she was unable to be about much. In December she noticed swelling of both legs and thighs. A cough developed and became gradually worse. Early in October, 1931, she began to have chilliness, sweats and fever. She entered Lakeside Hospital on November 27, with the additional statement that she had lost 11 pounds (4.9 Kg.) in the preceding two weeks. At this time the edema had disappeared. The heart showed marked enlargement to the right and left, and a systolic murmur over the pulmonary area was transmitted to the entire left lung. The lungs showed the signs of consolidation and cavitation in the left upper lobe. Blood pressure in the thigh was 146 systolic and 85 diastolic. During this period in the hospital the patient's temperature was generally between 38 and 40.1 C. (100.4 and 104.9 F.), the rises occurring in the late afternoon or evening, with one drop to 36.5 C. (97.7 F.) and two elevations to 41 C. (105.8 F.). The pulse rate was generally about 120, with a terminal elevation to 150. The respiratory rate fluctuated widely, but was generally about 30. The urine showed albumin, occasional erythrocytes and leukocytes and many casts. The output of phenolsulphonphthalein was 45 per cent in two hours. The leukocytes in the blood num-

bered 9,250 and 13,700; the differential counts showed a slight increase in polymorphonuclears. The erythrocyte counts were 3,390,000, 4,650,000 and 4,100,000, with no note on the character of these cells. The vital capacity was 1,800 cc. The spinal fluid was normal. A culture of the blood showed no growth. The stools were normal. The sputum contained many acid-fast bacilli. The blood for the Wassermann test was anticomplementary, but the Kline microprecipitation test was 4 plus positive. Roentgenologic examination at this time showed nothing significantly different from the former examination as regards the heart and great vessels, but the entire left lung showed irregularly distributed density, most marked in the upper portion, which was associated with cavitation. The right lung showed density in the peritruncal region. Electrocardiograms showed simple tachycardia and inversion of the T wave in lead III. The course during this stay in the hospital was progressively downward. Four days before death, symptoms of meningeal irritation appeared, but the fluid obtained by lumbar puncture was normal. The patient died on November 18.

Summary.—Nineteen months elapsed between the appearance of symptoms and death. It is suggested that syphilis was contracted at the time of the patient's marriage, thirteen years before death. It was reasonably established that the patient had syphilitic aortitis with either dilatation or aneurysm, and that at some time during the last nineteen months of life, tuberculosis of the lungs developed, which was especially manifest on the left side. The explanation of the to and fro murmur in the right carotid, the absence of pulse in the arteries of the arms and the later development of a systolic murmur of the pulmonic area, transmitted to the left lung, were the subject of much discussion. Doubt as to the presence of aortic aneurysm made it difficult to assume that an aneurysm was the cause of these disturbances, and it was suggested that there was congenital anomaly of the subclavian vessels.

After the actual condition was disclosed at autopsy, Dr. David Steele reviewed all the roentgenograms and found in one plate taken at a distance of 7 feet (213 cm.) in November, 1930 (fig. 1), that the obliteration of the cardiac incisura was distinguishable from that of the aortic knob by means of a shadow and because of the oblique views, probably not due to the left atrium. A shadow at the right hilus was indicative of dilatation of the right pulmonary artery. This plate also showed the first evidence of pulmonary tuberculosis. The findings are like those described in pulmonary artery dilatation by Balaban and Pokydow, considered adequate for a diagnosis by Vogl, and they conform to the picture of pulmonary hypertension given by Thomas.

Autopsy.—The autopsy, limited to the thorax and abdomen, was performed four hours after death by Dr. H. M. Dixon. The body was that of a fairly well nourished, well developed colored woman, approximately 28 years of age, 165 cm. in length and about 60 Kg. in weight. The body was still warm, showed slight rigor mortis of the extremities and no livor mortis. External examination showed nothing noteworthy except slight enlargement of the cervical lymph nodes and moderate edema of both feet and ankles, more marked on the left side.

The primary incision showed nothing noteworthy. The peritoneum and viscera were normal except that the liver extended 5 cm. below the costal margin. In the thorax the heart extended 3 cm. to the right of the midline and beyond the midaxillary line to the left. The left pleura was completely, and the right partly, obliterated by fibrous adhesions.

Cardiovascular System: The pericardial sac and fluid were normal. In the anterior mediastinum the great vessels were bound together by dense fibrous adhesions.

The heart was of globoid shape and, free from blood and clot, weighed 430 Gm. The epicardium and subepicardial fat were normal; the coronaries were not tortuous. The muscle was firm, cut with normal resistance and showed a slightly bulging, moist, uniformly dark red cut surface. The left ventricle was 7 cm. long and the wall 15 mm. thick. The right ventricle was 11 cm. long and the wall 4 mm. thick. The trabeculae carneae and the papillary muscles were large and slightly flattened. All four chambers appeared to be moderately enlarged, but this was most striking in the right ventricle. The mural and valvular endocardium was normal throughout, save for the pulmonary cusps to be described. The mitral orifice was 9 cm. in circumference, and the tricuspid 12 cm. The

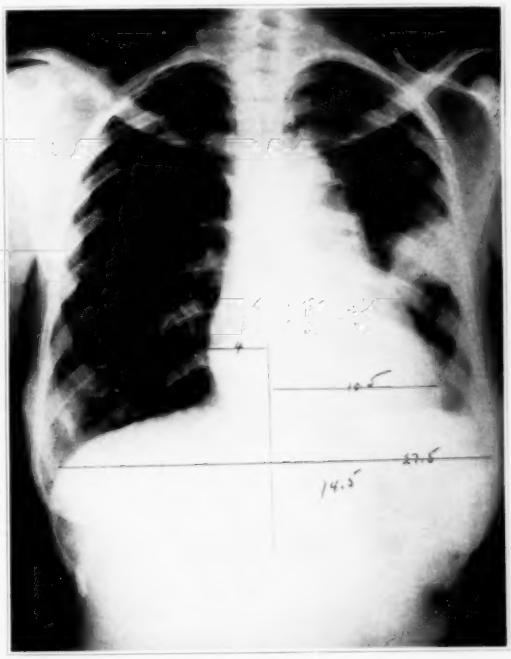

Fig. 1.—Roentgenogram taken at a distance of 7 feet following the patient's second admission. Note the obliteration of the cardiac incisura, the shadow of the right pulmonary artery and the shadows of tuberculous involvement of the left lung.

foramen ovale was closed and there were no gross lesions of the conduction system. The coronaries showed a few small plaques of thickened yellow and gray intima. The orifices were normally patent.

The aortic orifice measured 6 cm. in circumference, and the leaflets and sinuses of Valsalva were normal. The aorta was normal for a distance of from 4 to 5 cm. above the ring, save for a small plaque of intimal thickening from 3 to 5 mm. in diameter, elevated about 1 mm. above the surface, smooth, well defined and of a gray color, situated in the right posterior wall, 3 mm. above the junction of the anterior and right posterior leaflets. Beginning from 4 to 5 cm. above the ring the aortic circumference increased abruptly to a measurement of 8.2 cm. Beginning

at this region, in an irregular line extending horizontally around the aorta, the vessel showed the characteristic morphology of syphilitic mesaortitis, which terminated abruptly at the isthmus aortae, where the circumference was reduced to 4 cm. Beyond this the aorta measured 4.4 cm. in circumference and exhibited a moderate intimal atherosclerosis. In the syphilitic area two small saccular aneurysms were found, the orifice of each about 3 mm. in diameter. One in the inferior surface of the arch was 12 mm. deep, and the other in the posterior aspect was about 7 mm. deep. Both were filled with a thrombus. The innominate and left subclavian arteries at their origin showed markedly thickened walls, the lumen

Fig. 2.—Anterior view of the heart, showing dilatation of the aorta and pulmonary artery, disease of the branches of the aortic arch and occlusion of the left pulmonary artery.

was reduced to less than 1 mm. in diameter and the orifice of each was occluded by a thrombus. The left carotid orifice was similarly but less stenotic and without thrombus. The distal portion of these arteries was normal.

The pulmonary orifice was 8 cm. in circumference. The leaflets were thin, transparent and pliable. The arterial surface of the adjacent parts of the anterior cusps was closely applied by firm fibrous tissue to the arterial wall, so that this commissure was 8 mm. wide and exhibited a pale blue, thick, wrinkled intima. Beginning in the sinuses of Valsalva and extending through the entire main trunk of the pulmonary artery, there were the characteristic changes of syphilitic mes-

arteritis. The vessel was dilated in spindle form to a maximum circumference of 8.8 cm. The entire wall was thickened, and the intima showed pale blue hyaline plaques of thickening interspersed with areas in which there were stellate and parallel lines of depression, giving the usual wrinkled appearance. There were no localized dilatations, nor was there atheroma or calcification. At its ostium the left branch showed complete obliteration, which extended to the hilus of the lung. Viewed from the main trunk this ostium appeared as a small pitlike depression without a grossly observable lumen. A cross-section midway between the ostium

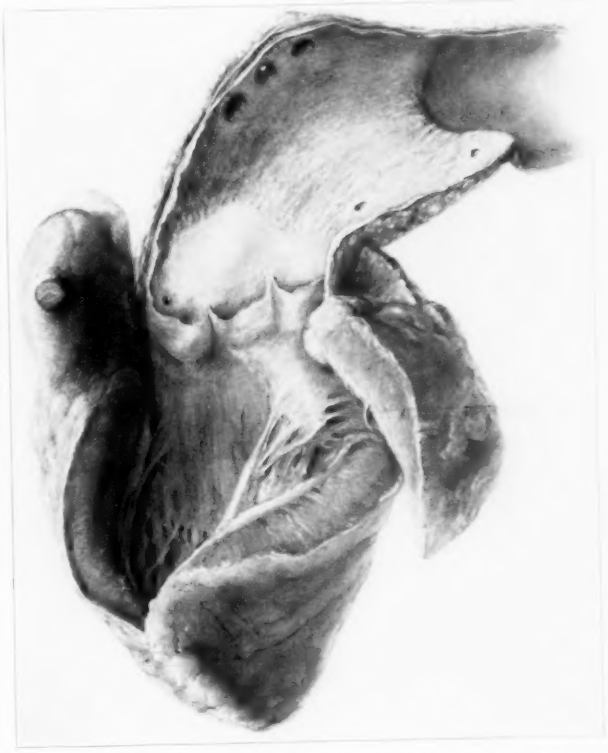

Fig. 3.—Interior of the left side of the heart and aorta. Note the occlusion of two of the branches of the aorta, partial occlusion of the third and dimples at the site of the two small aneurysms in the sharply delimited syphilitic mesaortitis.

and hilus showed the obliteration to be caused by dense, pale gray, fibrous tissue in which the intima could not be distinguished. The media was seen as a fairly regular pale yellow circle, interrupted by foci of tissue like that which obliterated the lumen. Marked adventitial and perivascular fibrosis bound the artery firmly to the veins and surrounding tissues. The obliteration ended abruptly at the division of the left pulmonary artery and was replaced by a partly occluding thrombus which extended a short distance into the branches. Grossly it appeared

to be partly organized, but microscopically the organization was only slight. The right branch showed the syphilitic process only at its origin. It was dilated to a diameter of 3 cm.

The right lung weighed 350 Gm., showed fibrous tags of adhesion on the surface, a small tuberculous cavity in the apex and slight passive hyperemia. The bronchi and hilar lymph nodes were not abnormal.

The left lung weighed 640 Gm., and was covered by extensive fibrous tags and moderately thickened pleura. The upper lobe showed extensive intercommunicating tuberculous cavities and caseous pneumonia. The lower lobe showed

Fig. 4.—Interior of the right side of the heart and pulmonary artery. Note the obliteration of the commissure between the anterior cusps of the pulmonic valve, typical syphilitic mesarteritis beginning in the sinuses of Valsalva and the dimple at the site of the orifice of the occluded left pulmonary artery.

a tuberculous cavity, 2 cm. in diameter. Aside from passive hyperemia there was nothing else noteworthy.

The abdominal viscera showed moderate passive hyperemia. Save for slight tortuosity of the tubes, the genitalia were normal.

A postmortem culture of the blood showed no growth.

Microscopic Examination: The aorta in the arch showed a thick fibro-hyaline intima, in which were a few fat spaces. The media showed numerous densely fibrous scars about the vasa vasorum, with slight infiltration of lymphoid cells (also a few plasma and large mononuclear cells) and moderate interruption of the

elastica. The adventitia was fibrous and edematous. The adventitial vasa vasorum showed chronic endarteritis and a moderate perivascular cellular infiltration. In the periarterial fat there was a moderate diffuse infiltration of lymphoid cells. In the neighborhood of the small aneurysms the medial and adventitial changes were much more severe. The depths of the aneurysms showed practically complete loss of media. The larger aneurysm contained a mature thrombus without organization. A section of the abdominal aorta showed intimal atherosclerosis without any indication of syphilis.

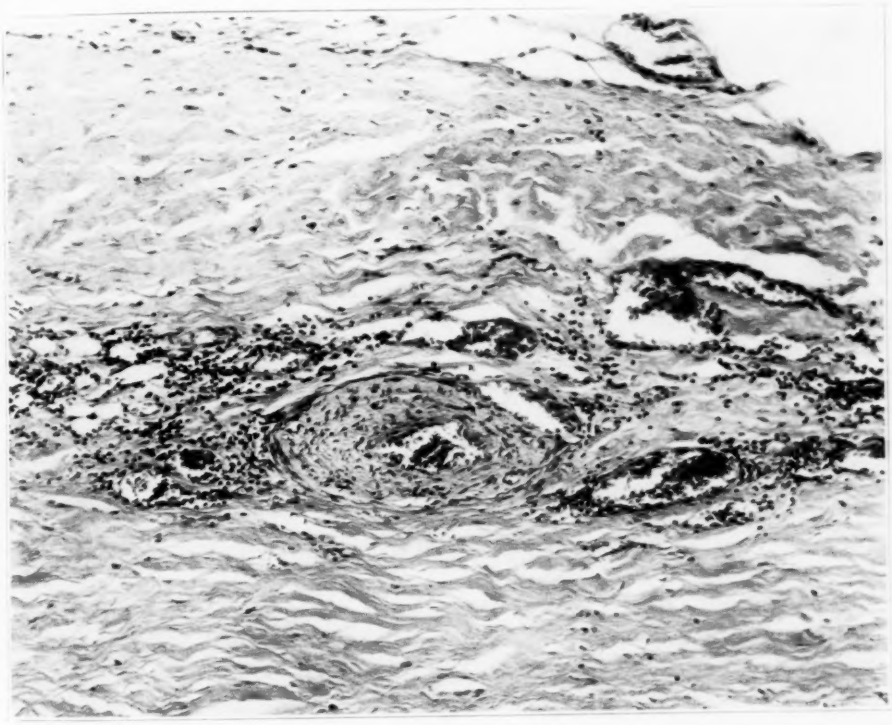

Fig. 5.—Perivascular round cell infiltration in the adventitia of the main stem of the pulmonary artery. Hematoxylin and eosin; × 158. Wratten green filter B 58.

The adventitia of the innominate artery showed intimal thickening of the vasa vasorum and extensive perivascular infiltration of lymphoid cells with a few plasma and large mononuclear cells. Where these vessels extended into the periphery of the media the same changes were noted. The media was of irregular thickness and showed a diffuse, and in a few places a focalized, infiltration of lymphocytes and a small number of large mononuclears. The intima was not distinguishable from a mass of collagenous connective tissue which filled the entire former lumen of the artery, sometimes densely and sometimes loosely arranged. Numerous

endothelial-lined blood vascular spaces of variable size were present, and two showed a thin musculo-elastic coat. Elastica stain showed only small fragments of the internal lamina and numerous interruptions in the elastica of the media. The central mass of fibrosis showed a few granules of blood pigment.

The subclavian artery showed essentially the same changes as the innominate, except that the tissue within the lumen was more loosely arranged, there were suggestions of fibrin remnants, the canalization was by larger vessels and the perivascular infiltration of lymphocytes was less marked.

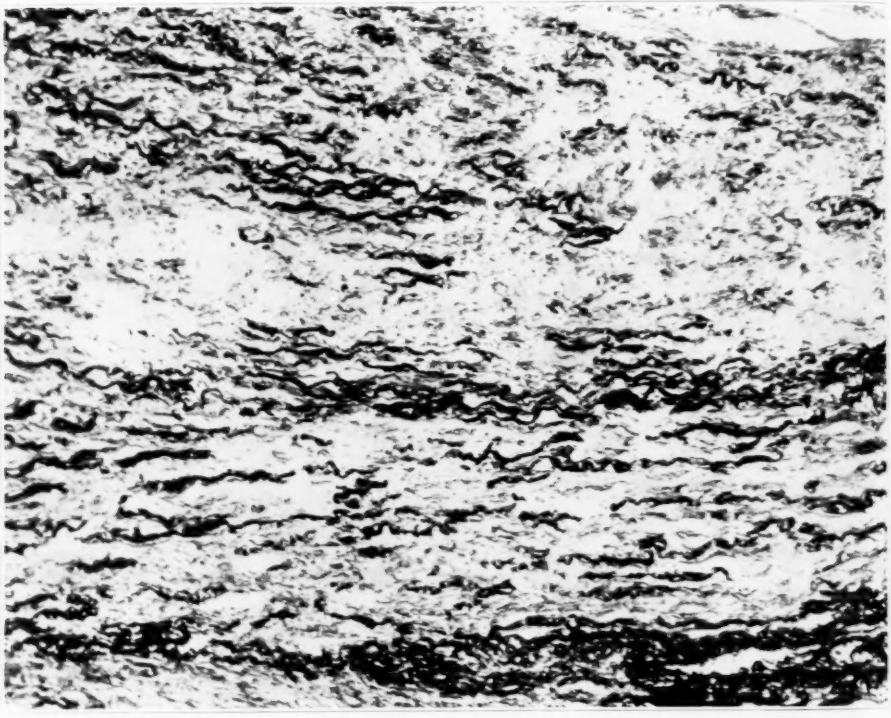

Fig. 6.—Fragmentation of the elastica of the main stem of the pulmonary artery. Verhoeff-Masson trichrome (acid fuchsin, ponceau de xylidine, licht Grün); × 117. Wratten orange filter E 22.

The pulmonary trunk showed marked thickening of the intima by fibrous connective tissue in which a few fat spaces and a small amount of mucoid tissue were observed. There was no clearly defined internal elastic membrane. The media showed a few areas of what appeared to be small fibrous scars and irregular areas of interruption of elastica. A few small areas of lymphoid cell infiltration often approximated the scars. The adventitial arteries showed intimal fibrosis and moderate perivascular lymphoid cell infiltration. The intrapulmonic branches,

from 0.5 to 1 mm. in diameter, showed moderate intimal fibrosis. The branches, of about arteriolar and slightly larger size, in the neighborhood of the tubercles only, showed a loosely fibrous thickened intima with lymphoid cell infiltration of the media and intima, but this was not general throughout the lungs.

The left main branch was sectioned at two levels in the area of occlusion. The lumen in one section was filled with hyalinized fibrous tissue with a few granules of blood pigment, and in the other with dense connective tissue in which there were a few endothelial-lined blood channels. Otherwise the sections were similar.

Fig. 7.—Perivascular and perineurial round cell infiltration in the adventitia of the left pulmonary artery. Hematoxylin and eosin; × 158. Wratten green filter B 58.

The internal elastic lamina was present only as small fragments, some of which were swollen. The elastica of the media showed large areas of interruption and disappearance, and many fragmented fibrils were swollen. The interruption of elastica was by a mass of fibrous tissue with many fibroblasts, small blood vessels of capillary size and a diffuse infiltration of lymphoid cells, a few plasma cells, many large mononuclears and a notable number of polymorphonuclear cells, the whole giving the impression of a granulation tissue. The adventitia showed heavy masses of dense fibrous, partly hyaline, connective tissue. The vasa vasorum

showed variable degrees of intimal fibrosis. Marked perivascular and perineurial infiltration of lymphoid, plasma and large mononuclear cells was present.

Sections stained by a modification of the Warthin-Starry method, which showed spirochetes in controls of syphilitic fetal liver and syphilitic testis of the rabbit, failed to demonstrate spirochetes in any of this material.

The myocardium showed large muscle nuclei with square ends, loss of muscle striations and attenuation of the fibers, and a diffuse fibrosis, slight in extent and somewhat more marked about the vessels, with a few lymphoid and plasma cells. The lesions showed no definite characteristics of syphilitic myocarditis. The coro-

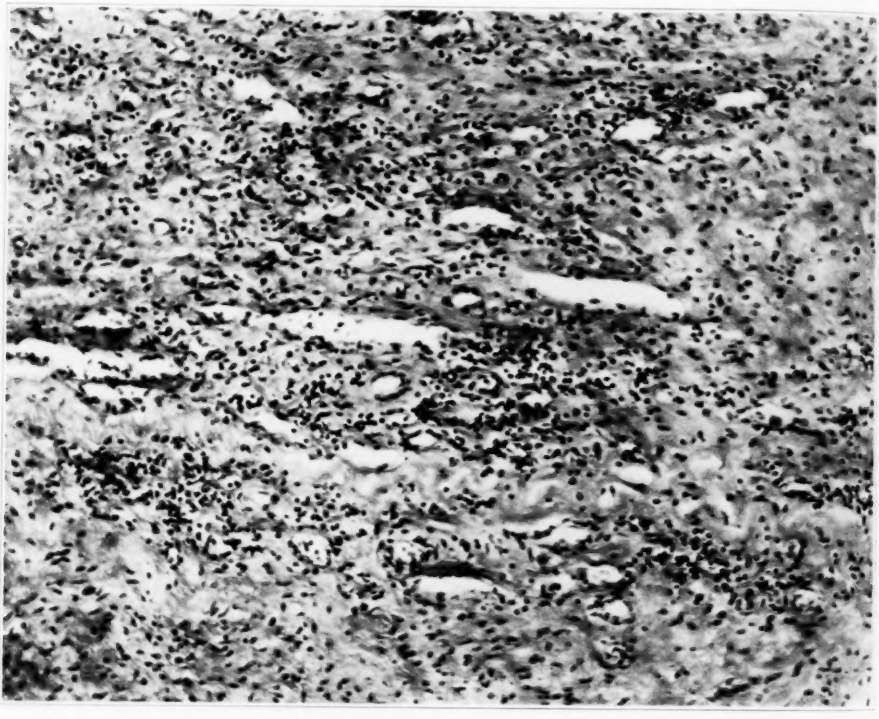

Fig. 8.—Diffuse round cell infiltration of the media of the left pulmonary artery. Hematoxylin and eosin; × 158. Wratten green filter B 58.

nary arteries were sectioned at various levels, including a point within 2 cm. of the orifice, and although showing definite intimal fibrous sclerosis they exhibited none of the changes described by Moritz in syphilitic coronary arteritis.

The lungs showed characteristic tubercles, tuberculous caseation and well marked passive hyperemia. The branches of the pulmonaries have already been described. The pleura of the left lung was markedly thickened by fibrous connective tissue, somewhat loosely arranged and with a slight diffuse infiltration of lymphocytes. Especially notable was a rich vascularization of visceral and parietal

pleura in all sections from the left side. The vessels were extremely numerous and many were well differentiated into small arteries and veins.

The other organs, especially the liver, spleen and kidneys, showed a much more marked passive hyperemia than was evident in the gross specimens.

Summary.—The significant autopsy findings were marked syphilitic arteritis of the arch of the aorta and the main trunk of the pulmonary artery.[2] In the aorta the process was accompanied by fusiform dilatation, small saccular aneurysms and syphilitic arteritis of the three branches from the arch with completely organized,

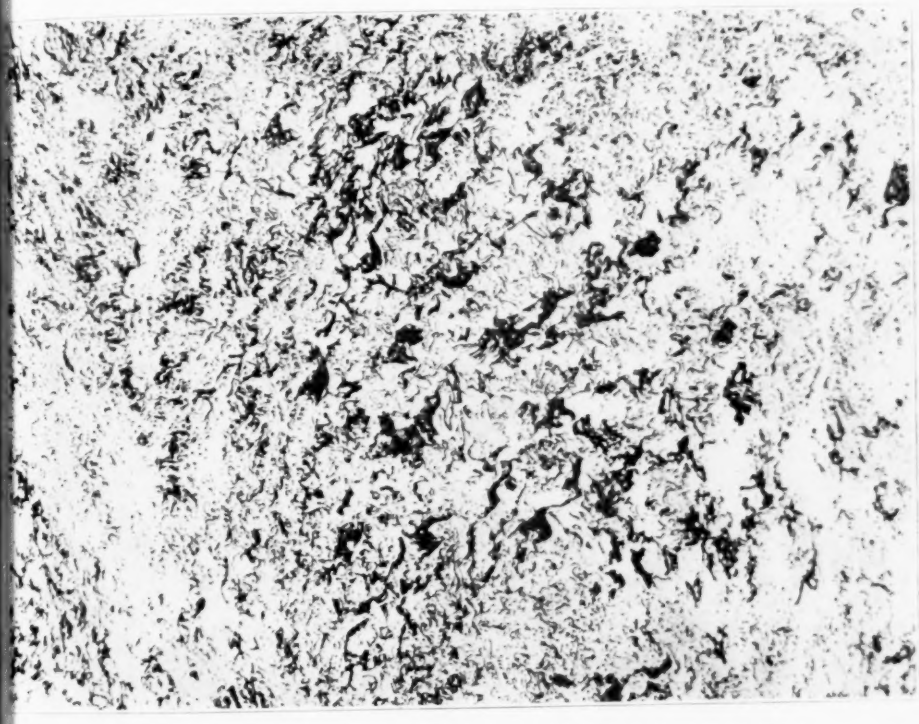

Fig. 9.—Fragmentation and swelling of elastica of the media of the left pulmonary artery. Verhoeff-Masson trichrome (as in figure 6); × 117. Wratten orange filter E 22.

cicatrized, canalized thrombosis of the innominate and subclavian arteries. In the pulmonary artery the process was accompanied by fusiform dilatation, organized

2. The morphologic diagnosis is as certain in the pulmonary artery as in the aorta. With his skill and excellent technic Warthin was able to demonstrate spirochetes, but in the other cases they have not been found. In the present case the demonstration failed, but the morphologic evidence is so definite as to leave no doubt of the diagnosis.

canalized thrombosis of the left branch and dilatation of the right branch. Most careful examination failed to disclose enlargement of the bronchial arteries. There was moderate hypertrophy of the heart, especially manifest in the left ventricle and also present in the right ventricle, associated with cardiac dilatation, generalized, well marked passive hyperemia and, in the lower extremities, also with edema. There was chronic ulcerative pulmonary tuberculosis, especially marked on the left side. There was extremely rich vascularization of the obliterated left pleura. Gumma formation was not noted in any part of the body. The death of the patient was determined principally by the pulmonary tuberculosis and a moderate congestive heart failure.

Correlation.—The symptoms on the first admission were in part those of congestive heart failure. The coldness and numbness of the upper extremities, together with absence of arterial pulsation, were due to disease of the arteries derived from the arch of the aorta. The pulsation of the right carotid artery with the to and fro murmur may have been related to incomplete occlusion of the innominate artery at that time. The systolic murmur at the cardiac apex probably belongs among the murmurs of that type frequent in dilated hearts. A to and fro murmur over the aortic area was suspected but not definitely established, and was not recorded during the second stay in the hospital. The development of ulcerative pulmonary tuberculosis was accompanied by the usual cough, chilliness, night sweats, rapid loss of weight, elevated pulse and respiratory rates and reduction of vital capacity. The last sign may have been due in part to passive hyperemia of the lungs. After the second admission a systolic murmur was heard over the pulmonic area, probably due to dilatation of the main stem of the pulmonary artery. The transmission to the left lung may have been determined in part by the solidification of the left pulmonary artery and in part by the tuberculous consolidation in the lung. It is noteworthy that with definite separation of one of the pulmonic commissures there was no diastolic murmur, because the valve must have been incompetent. The inversion of the T wave in lead III is not satisfactorily explained, since the hypertrophy of the right ventricle was only moderate as compared with that of the left ventricle. In cases in which the smaller pulmonary arteries are narrowed and the right ventricle notably hypertrophic, clearcut right axis deviation has been reported, but these anatomic changes were not present in this case. Anemia was not severe at any time. There was no secondary polycythemia and no reason disclosed at autopsy why there should have been. It is possible that had clinical attention been drawn to disease of the pulmonary artery, the roentgenologic examination might have been interpreted as showing dilatation of the main stem of the pulmonary artery in addition to dilatation of the aorta.

COMMENT

It may well be true that in the later stages of syphilitic disease and of atherosclerosis of the pulmonary artery, Warthin's statement that the two lesions are difficult to distinguish is valid. In the accepted cases of syphilis, however, the condition of the pulmonary artery is such that the distinction can readily be made. As a rule the perivascular cellular infiltration in the media is less severe than is common in aortic syphilis; yet many cases of the latter disease show medial changes which are no different in this respect from those occurring in the pulmonary

artery. Adventitial perivascular cellular infiltration is quite as marked as that observed in the aorta. The condition of the internal elastic membrane varies in syphilitic aortitis, but the variation seems to be greater in the same disease of the pulmonary artery. In the cases described in detail this membrane may be intact, fragmented or completely lost. The medial elastic lamellae are interrupted in both instances. The swelling of elastica fragments with the formation of spider-like bodies is more marked in the case described here than is ordinarily observed in syphilitic aortitis. Granulation tissue with new blood vessel formation in the media is especially notable in the occluded left pulmonary artery in this case, but this may have been due to the action of the thrombus as a foreign body rather than to the syphilitic character of the arterial disease. In general, it can be asserted that productive-cicatricial syphilitic lesions of the pulmonary artery show essentially the same changes as those observed in syphilitic mesaortitis.

Of the cases of syphilitic productive-cicatricial disease of the pulmonary artery accepted in this paper, association with similar disease of the aorta is noted in six instances and freedom from aortic lesions in four instances. The question arises as to whether or not the lesion of the pulmonary artery in the case here reported represents extension from the aortic disease. In fifty-nine cases of aortic syphilis Sindoni found extension to the pulmonary artery in nine. With one exception, the disease in the pulmonary artery was slight and often confined to the adventitia. It is noteworthy in the present case that the part of the aorta in closest contact with the pulmonary artery was free from aortitis. No final conclusion can be reached, but the anatomic evidence in this case is against rather than in favor of the conception of extension from the aorta.

If aneurysm be defined as a permanent dilatation of a vessel, all the cases exhibited this lesion, of a cylindric, fusiform or saccular variety. If the dilatation must be sharply localized, only three of the eleven cases showed aneurysm formation. The significant fact is that the disease in the pulmonary artery in all cases led to dilatation of the vessel, either general or localized or both. Although pulmonary hypertension may produce dilatation of the pulmonary artery and its larger branches, as indicated by Thomas, there is no reason for assuming that this is of importance in the dilatation of the main branch in productive-cicatricial syphilis, except when additional extensive disease of the smaller arteries can be demonstrated. Henschen argued that since most aneurysms of the pulmonary artery occur between 24 and 42 years of age, and since arteriosclerosis before the age of 42 is usually due to syphilis, it can be supposed that the aneurysms are syphilitic. Posselt thought that this might well be an exaggeration. In the cases of productive-cicatricial syphilis of the pulmonary artery accepted here, six of the patients were

42 years old or less and five were more than 42 years old, which in no sense supports Posselt. A true saccular aneurysm of the pulmonary artery in a man, 31 years old, without any evidence of syphilis was reported by Okkels and Thierkelsen. It seems justifiable to suggest that although aneurysm of the pulmonary artery is frequent in syphilis, it may perhaps be relatively more often a result of atherosclerosis than is aneurysm of the aorta.

Thrombosis is proportionately much more common in association with syphilis of the pulmonary artery than in similar disease of the aorta. Of the three cases of saccular aneurysm, thrombosis was noted in two, namely in those of Henschen and Warthin. Of the other eight cases, thrombosis was noted in five, namely those of Ploeger, Letulle and Jacquelin, Thomas, Plenge (one case) and me. The clot varies from a relatively fresh mass to complete organization and cicatrization. It cannot be said that the roughening of the intima is any greater in the disease of the pulmonary artery than in that of the aorta; there is no clear statement that the physical state of the blood is different, and hence the thrombosis is probably due to a slower flow of blood in the pulmonary than in the systemic circulation, which is emphasized locally by dilatation. The same inference may be drawn from the instances of thrombosis in apparently nonsyphilitic sclerosis, as in the six cases of Brenner and in those of Frothingham, of Jump and Baumann, of Means and Mallory and of others.

Complete occlusion of the right branch was found in the case of Letulle and Jacquelin, and was due to an organized occluding thrombus. In Henschen's case the right pulmonary branch was markedly stenotic as the result of thickening of the walls. In Barth's case the right branch was narrowed to the size of a lead pencil, apparently from surrounding cicatrization. In Ploeger's case the organized thrombus of the main stem extended into both branches, but patent lumens were observed without note as to diameter. In the case herewith reported the left branch was completely occluded by fibrosis, the result of an old thrombus. Although details are lacking in some of the cases reported, the occlusion of a branch of the pulmonary artery is due in large part to the organization and cicatrization of thrombi. If it is remembered that syphilitic aortitis is often accompanied by narrowing of the ostia of coronaries and large arteries of the arch, it cannot be said that syphilis of the pulmonary artery appears to be more often accompanied by limitation of the lumens of its branches than is syphilitic aortitis; yet the actual occlusion by thrombosis and subsequent fibrosis seems to be more frequent in connection with syphilis of the pulmonary artery than with syphilis of the aorta. In the present case the occlusion of the innominate and left common carotid appears to be due to an organized thrombus, but that this may have been secondary to disease of the walls is indicated

by the stenosis of the left subclavian artery. That similar occlusion of a branch of the pulmonary artery may be secondary to intimal atherosclerosis is illustrated by the case of Means and Mallory.

The changes in a lung incident to complete occlusion of its main artery are less marked than might be expected. In the cases of Henschen, Barth and Ploeger, in which the lumen was still patent, there were no changes in the lungs that could be definitely attributed to circulatory disturbance. In the case of Letulle and Jacquelin the right branch was completely occluded and the lung showed passive hyperemia. The authors made no note of the collateral circulation. In the case of non-syphilitic occlusion reported by Means and Mallory the bronchial arteries were much enlarged. In the case reported here the bronchial arteries were not enlarged, but the obliterated thickened pleura showed an extraordinarily great number of blood vessels, some of which were differentiated into small arteries. In the absence of enlarged bronchial arteries, it is suggested that the collateral circulation was provided through the richly vascularized adherent pleura. It is not likely that a large amount of collateral circulation is necessary for the maintenance of nutrition of the lung substance. Pleural vascularization was noted by Barth, but this was on the left side, and the left pulmonary artery was apparently not occluded.

Statistically, the association of tuberculosis with stenosis or occlusion of the pulmonary artery cannot be established. It is of interest that in Henschen's case the partial occlusion was associated with extensive pleural synechiae and with tuberculous cavities in that lung. In Barth's case the lung on the affected side was normal. In Ploeger's case, in which both pulmonary branches were partly occluded, the right lung was normal, but the left showed old tuberculosis and bronchiectasis. In the case of Letulle and Jacquelin, both lungs showed miliary tuberculosis, but the lung in which the artery was completely occluded showed extensive tuberculous cavitation. In the case reported here the lung in which the artery was occluded showed not only tuberculosis but, on clinical observation, a rapidly progressing lesion. The opposite lung showed relatively little tuberculosis. In Means and Mallory's case tuberculosis was not observed unless a necrotic partly calcified mass, presumably interpreted as old infarct, may have been tuberculous. The suggestion is plain that occlusion of the pulmonary artery may be of significance in the development or extension of tuberculosis in the lung.

Hypertrophy of the heart, especially manifest in the right ventricle but variable in degree, has been observed in all the cases reported. When a diffuse disease of the small pulmonary arteries and arterioles is present, the hypertrophy may be due to pulmonary hypertension. When such disease is not demonstrated, it is difficult to explain the

hypertrophy because there is no reason for assuming that dilatation or aneurysm of the pulmonary artery brings about cardiac hypertrophy when such a result does not follow similar disease in the aorta. The cardiac hypertrophy in the present case is certainly not due to diffuse vascular disease in the lungs. It is probably not caused by the occlusion of the left branch of the pulmonary artery, since it has been shown physiologically by Daly and by Gibbon, Hopkinson and Churchill that 60 per cent of the cross-sectional area of the pulmonary circulation may be obliterated without effect on the arterial or venous pressure. The widening of one commissure of the pulmonic valve may well have predicated an insufficiency, which could serve to explain the observed hypertrophy.

CONCLUSION

Productive-cicatricial syphilitic disease of the pulmonary artery, i. e., of the Döhle-Heller type, is extremely uncommon, but occurs often enough to justify its consideration in clinical diagnosis. Eleven cases, anatomically proved by reasonably liberal interpretation, are now on record. Eight of these would be regarded as clearly established by the most exacting criteria. Gummatous types of lesion about equal the productive-cicatricial type in incidence, but this ratio may be changed as additional cases are reported. The proportion of productive-cicatricial to gummatous lesions is markedly higher in the aorta than in the pulmonary artery. All cases of productive-cicatricial lesions in the main stem of the pulmonary artery show local or diffuse dilatation of the vessel. Associated disease of the smaller pulmonary arteries is by no means constant, but all cases have shown some degree of cardiac hypertrophy. Thrombosis is more frequently associated with productive-cicatricial lesions of the pulmonary artery than with the same lesions of the aorta. The anatomic character of the lesion, as it affects both aorta and pulmonary artery, is essentially the same, although it is probable that in the pulmonary artery the internal elastic lamina is more severely affected than in the aorta. Both aorta and pulmonary artery show productive-cicatricial lesions in about half the cases, but this does not of necessity mean that the disease in one vessel is an extension from the lesion in the other vessel.

The disease affects the sexes about equally, and has been found at the age extremes of 28 and 58 years, with the maximum incidence in the sixth decade. It is associated with cardiac difficulties and ultimately congestive heart failure, and may exhibit a fairly characteristic roentgenogram. The most frequent murmur is a systolic murmur over the pulmonic area. Occlusion of a main branch of the pulmonary artery appears to have some relation to development and progress of pulmonary tuberculosis on the affected side.

BIBLIOGRAPHY

Balaban, J. J., and Pokydow, M. J.: Zur Diagnostik der Aneurysmen der Lungenarterie, Röntgenpraxis **1**:454, 1929.

Barth, H.: Ein Fall von Mesarteritis luetica der Arteria pulmonalis mit Aneurysmenbildung, Frankfurt. Ztschr. f. Path. **5**:139, 1910.

Brenner, O.: Sclerosis of the Pulmonary Artery with Thrombosis, Lancet **1**:911, 1931.

Daly, I. deB.: The Resistance of the Pulmonary Vascular Bed, J. Physiol. **49**: 238, 1930.

Darré, H., and Albot, G.: Une forme de syphilis du poumon: sclérose syphilitique nodulaire avec panartérite pulmonaire, Ann. d'anat. path. **5**:861, 1928.

Frothingham, C.: A Case of Extensive Bilateral Progressive Thrombosis of the Smaller Branches of the Pulmonary Artery, Am. J. Path. **5**:11, 1929.

Gibbon, J. H.; Hopkinson, M., and Churchill, E. D.: Changes in Circulation Produced in Gradual Occlusion of the Pulmonary Artery, J. Clin. Investigation **11**:543, 1932.

Hare, D. C., and Ross, J. M.: Syphilitic Disease of the Pulmonary Arteries, with Account of a Case, Lancet **2**:806, 1929.

Henschen, S. E.: Das Aneurysma arteriae pulmonalis, Samml. klin. Vortr., 1906, no. 422-423 (Inn. Med. no. 126-127, 595-655).

Jump, H. D., and Baumann, F.: Large Thrombus of the Pulmonary Artery with Chronic Cyanosis and Polycythemia, Pennsylvania M. J. **32**:754, 1929.

Karsner, H. T.: Pulmonary Arteries, in Survey on Arteriosclerosis, Josiah Macy, Jr., Foundation, to be published.

Letulle, M., and Jacquelin, A.: Anévrismes syphilitiques de l'artère pulmonaire, Arch. d. mal. du cœur **13**:385, 1920.

Means, J. H., and Mallory, T. B.: Total Occlusion of the Right Branch of the Pulmonary Artery by an Organized Thrombus, Ann. Int. Med. **5**:417, 1931.

Moritz, A. R.: Syphilitic Coronary Arteritis, Arch. Path. **11**:44 (Jan.) 1931.

Okkels, H., and Thierkelsen, F.: Ein Fall von Atherosklérosis pulmonalis mit Aneurysma Arteria pulmonalis bei offenstehen des Foramen ovale, Acta path. et microbiol. Scandinav. **9**:214, 1932.

Peck, S.: Pathologic Anatomy of Syphilis of the Pulmonary Artery: Report of a Case and Review of the Literature, Arch. Path. **4**:365 (Sept.) 1927.

Plenge, K.: Zur Frage der Syphilis der Lungenschlagader, Virchows Arch. f. path. Anat. **275**:572, 1930.

Ploeger, A.: Das Aneurysma der Arteria pulmonalis, Frankfurt. Ztschr. f. Path. **4**:286, 1910.

Posselt, A.: Die Erkrankungen der Lungenschlagader, Ergebn. d. allg. Path. u. path. Anat. **13**:298, 1909.

Reeke, T.: Ueber Syphilis der Pulmonalarterie, Centralbl. f. allg. Path. u. path. Anat. **49**:257, 1930.

Rogers, L.: Extensive Atheroma and Dilatation of the Pulmonary Arteries, Without Marked Vascular Lesions, as a Not Very Rare Cause of Fatal Cardiac Disease in Bengal, Quart. J. Med. **2**:1, 1908-1909.

Rosenthal, S. R.: Sclerosis of the Pulmonary Artery and Arterioles, Arch. Path. **10**:717 (Nov.) 1930.

Sindoni, M.: Sulla sifilide dell'arteria pulmonare, Arch. ital. di anat. e istol. path. **1**:629, 1930.

Thomas, M.: Contribution à l'étude des affections acquises de l'artère pulmonaire, Thèse de Paris, 1927.

Vogl, A.: Ein Fall von luischem Aneurysma der Arteria pulmonalis, Med. Klin. **27**:1352, 1931.

Warthin, A. S.: Syphilis of the Pulmonary Artery, Am. J. Syph. **1**:693, 1917.

EFFECT OF DRUGS ON CARDIAC STANDSTILL INDUCED BY PRESSURE ON THE CAROTID SINUS

M. H. NATHANSON, M.D.
MINNEAPOLIS

In 1866 Czermack [1] demonstrated that digital pressure of the neck in the region of the vagus nerve caused a slowing of the heart rate in man. He attributed this effect to a mechanical excitation of the vagus nerve. Hering,[2] while making observations on this phenomenon, noted that very slight pressure resulted in marked cardiac inhibition in some instances. These observations led him to doubt the theory of direct vagal stimulation. Hering and his co-workers demonstrated conclusively that the slowing of the heart by digital pressure in the neck was the result of a reflex which originated in a specialized portion of the internal carotid artery, the carotid sinus. It has been observed that the usual response to pressure on the carotid sinus is a moderate slowing of the heart rate, but that in some instances there results a complete arrest of the heart for many seconds. The present report consists of a study of the effect of drugs on patients with prolonged cardiac standstill induced by sinus caroticus pressure.

In a study of the effect of pressure on the sinus caroticus and of the significance of various disturbances in the cardiac mechanism, it was noted that many persons responded repeatedly with a constant type of reaction. This consisted of a prolonged cardiac arrest due to the vagal inhibition of the sinus node. In some subjects this type of response occurred at times while at other times the period of inactivity of the sinus node was interrupted by the formation of new centers of impulse initiation in the junctional tissues or in the ventricles. It was apparent that the prolonged cardiac arrest in the first group depended on two factors: (1) the temporary suppression of the sinus node, depriving the heart of its normal pacemaker, and (2) the failure of formation of new foci of impulse initiation. The elimination of the cardiac standstill might be accomplished by the application of drugs affecting either of

From the Department of Medicine, University of Minnesota, Medical Service, Minneapolis General Hospital.

1. Czermack, J. N.: Ueber mechanische Vagusreizung beim Menschen, Jenaische, Ztschr. f. med. u. Naturw. **2**:384, 1866.

2. Hering, H. E.: Die Karotissinus-Reflexe auf Herz und Gefässe, Dresden, Theodore Steinkopff, 1927.

these factors. Since the inactivity of the sinus node is due to a reflex stimulation of the vagus nerve, the first factor may be approached by the use of atropine. It was apparent that the cardiac arrest might also be abolished by the use of drugs that would tend to increase the function of rhythmicity of the heart muscle, leading to the formation of new centers of impulse initiation.

The subjects who show no tendency toward a spontaneous formation of ectopic rhythmic centers during the suppression of the sinus node permit a direct and objective study of the effect of drugs on the function of cardiac rhythmicity. If the application of a drug abolishes the prolonged cardiac arrest by inducing an ectopic rhythm, it is reasonable to conclude that this drug increases the rhythmic property of the cardiac muscle. The method used in the present study consisted of a control period of observation, recording with electrocardiograms the effect of stimulation of the carotid sinus. Although the effect of stimulation of both carotid arteries was observed, the right carotid sinus was used in the pharmacologic studies, as this produced the more marked reaction. The drug was then administered, and after a suitable period an electrocardiogram was taken again, the effect of stimulation of the carotid sinus being observed. A week usually elapsed between each group of experiments to allow the effect of the previous procedures to pass off. The following drugs were used: atropine, epinephrine hydrochloride, ephedrine, barium chloride, calcium gluconate, digitalis and caffeine.

Subjects showing prolonged cardiac standstill on pressure on the carotid sinus are encountered most commonly among the elderly patients with cardiac disease attending an outpatient clinic. The pharmacologic studies were carried out on a number of such subjects, but most of the observations were made on a patient who was especially favorable for this type of investigation. This subject, H. B., was a man, 70 years of age, who suffered from mild anginal attacks and showed electrocardiographic evidence of coronary disease. Slight compression of the right carotid sinus repeatedly elicited a constant response, which consisted of a period of cardiac standstill varying from 7 to 9 seconds. The electrocardiogram showed no evidence of either auricular or ventricular activity during this period. This reaction could be elicited without discomfort to the patient, and on successive repetitions of the pressure there was no variation in the response. A period of control observation of several months demonstrated a remarkable constancy in the type of reaction (fig. 1). The response to pressure on the carotid sinus was almost immediate, and the period of cardiac standstill never exceeded nine seconds, although the pressure was applied for from ten to fifteen seconds. After the cardiac standstill, there was consistently a normal first beat originating

in the sinus node. This was frequently followed by a single extrasystole. In none of the control records was there any indication of an ectopic beat during the period of stimulation of the carotid sinus. The other subjects who were observed fulfilled the same requirements, with the exception that there was a shorter period of control observation.

EFFECT OF DRUGS

Atropine.—The effect of atropine is illustrated in figure 2. The heart rate varied between 50 and 58 before the administration of the drug. Pressure on the right carotid sinus elicited a cardiac standstill of 7.2 seconds. A subcutaneous injection of atropine sulphate, 2 mg., was given. Twenty minutes after the administration of the drug the heart rate was 68. Pressure on the right carotid sinus resulted in no change in the cardiac rhythm. The fact that the cardiac inhibition is

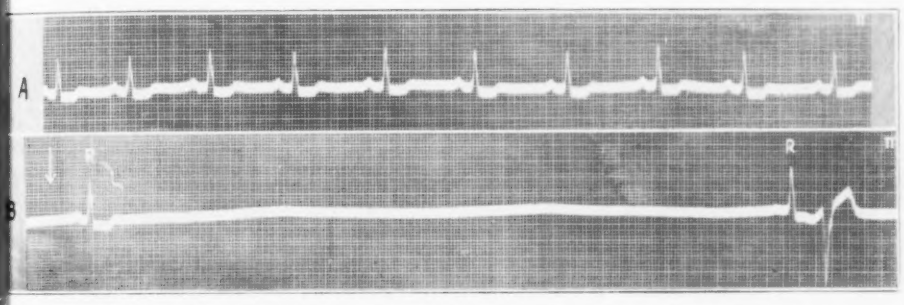

Fig. 1 (patient H. B.).—Lead 2 of a typical control record. *A*, before pressure on the carotid sinus; *B*, the effect of pressure on the right carotid sinus shown at arrow; cardiac standstill of 8.8 seconds.

abolished by paralysis of the vagus nerve indicates that this nerve is the sole efferent path of the reflex. Hering, by the use of atropine and by vagotomy, has demonstrated this in experimental animals.

Epinephrine.—The effect of epinephrine was observed in five cases. The results in the subject H. B. are illustrated in figure 3. Before the administration of the epinephrine, pressure on the right carotid sinus elicited a cardiac arrest of 7.5 seconds (fig. 3 *B*). Fifteen minutes after the subcutaneous injection of 1 cc. of epinephrine hydrochloride, 1:1,000, another electrocardiogram was taken following the application of pressure to the carotid sinus (fig. 3 *C*). It is to be noted that the P wave disappears, and that there is a slight alteration in the ventricular portion of the complex. It is apparent that an idioventricular rhythm has developed from a focus near the auriculoventricular node under the influence of the epinephrine. The rate of the ectopic rhythm is 48, as compared with the sinus rate of 60 a minute. This experiment was

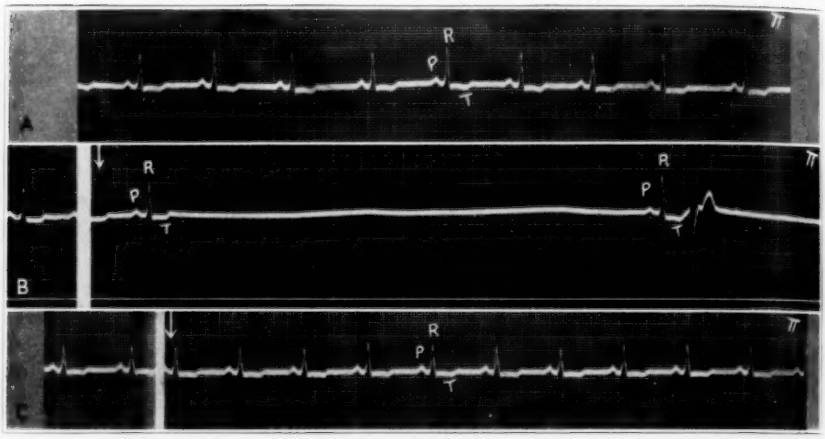

Fig. 2 (patient H. B.).—Lead 2. *A*, before pressure on the carotid sinus; *B*, pressure on the right carotid sinus, with cardiac standstill of 7.2 seconds; *C*, abolition of the carotid sinus reflex after the administration of atropine sulphate.

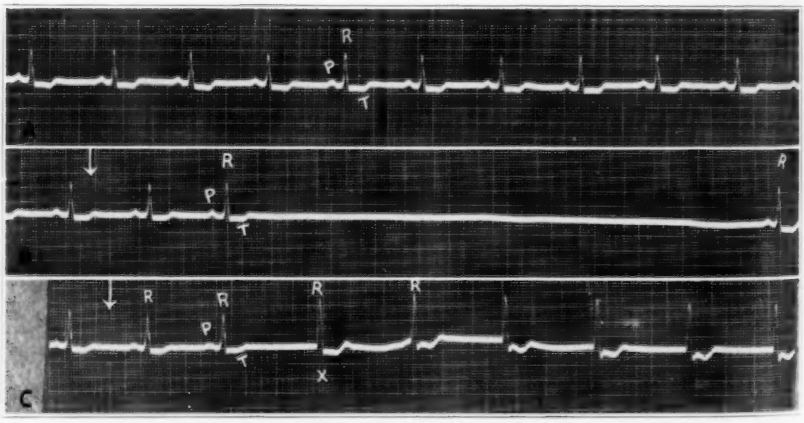

Fig. 3 (patient H. B.).—*B*, the effect of pressure on the right carotid sinus; *C*, compression of the right carotid sinus after the administration of epinephrine, showing the development of an idioventricular rhythm at *X*.

repeated on the subject H. B. on four later occasions, with the same results, the ectopic ventricular beats having approximately the same appearance as those in the first experiment. Four other subjects were studied in the same manner, and in each instance epinephrine abolished a prolonged cardiac standstill by the initiation of a ventricular rhythm (figs. 4, 5 and 6). These results confirm the many observations which indicate that epinephrine increases the rhythmic function of the cardiac

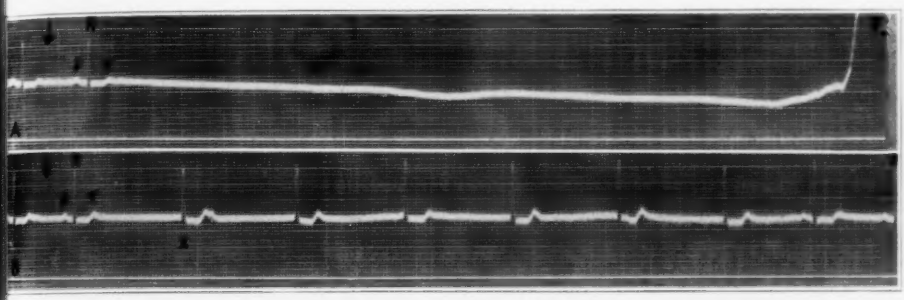

Fig. 4 (patient E. M.).—*A*, the effect of pressure on the right carotid sinus; cardiac standstill of 10.4 seconds with the development of an Adams-Stokes seizure. *B*, after the administration of epinephrine, pressure on the right carotid sinus induces a nodal rhythm at *X*.

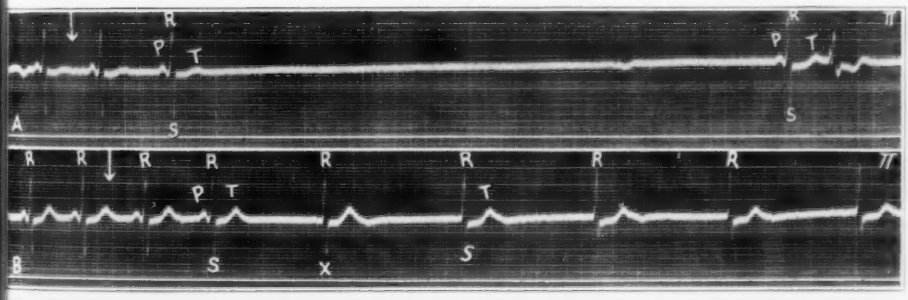

Fig. 5 (patient J. T.).—*A*, a cardiac arrest of 8.2 seconds after right carotid sinus pressure. *B*, the effect of right carotid sinus pressure after the administration of epinephrine, with the onset of nodal rhythm shown at *X*.

muscle. This may be due in part to a direct effect on the muscle, since epinephrine increases the rate of a denervated heart, and in part to a stimulation of the accelerator nerves. Rothberger and Winterberg[3]

3. Rothberger, C. J., and Winterberg, H.: Ueber die experimentalle Erzeugung extrasystolischer ventrikulärer Tachykardie durch Accelleransreizung, Arch. f. d. ges. Physiol. **142**:461, 1911.

found that ventricular rhythm could be produced by stimulation of the left sympathetic nerve if the right vagus was stimulated at the same time. Hering [4] destroyed the auriculoventricular bundle, and noted that the stimulation of the accelerators increased the rate of the ventricles. Cullis and Tribe [5] demonstrated that small doses of epinephrine increase the rate of auricles and ventricles both before and after section of the auriculoventricular bundle. Since 1916 there have been a number of clinical reports indicating that epinephrine has a favorable effect in preventing the Adams-Stokes seizures of heart block. The present experiments definitely indicate that epinephrine has a powerful effect on the impulse-initiating mechanism of the ventricles.

In the subject H. B. an attempt was made to study the duration of the effect of epinephrine. An electrocardiogram was taken, and pres-

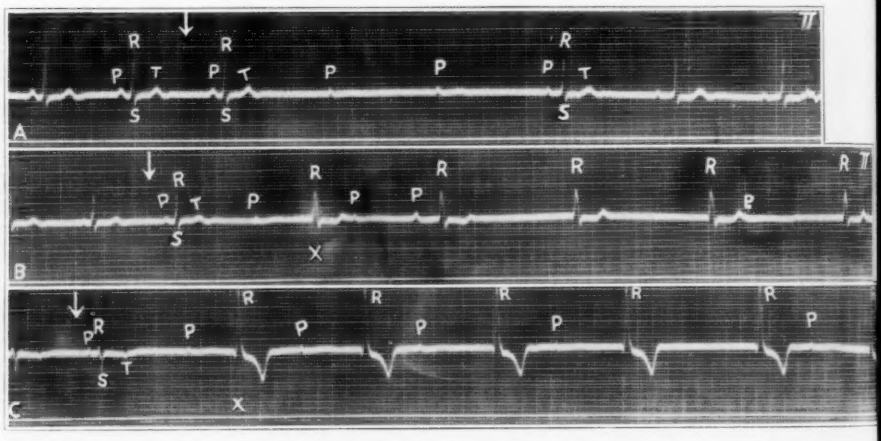

Fig. 6 (patient M. Y.).—*A*, lead 2, showing auriculoventricular block with ventricular standstill of 4.5 seconds after pressure on the right carotid sinus. *B*, lead 2, pressure on the right carotid sinus after the administration of epinephrine, with the onset of slow ventricular rhythm shown at *X*. *C*, lead 3, showing that the origin of the ectopic rhythm is in the left ventricle (new terminology).

sure on the right carotid sinus elicited in this instance a cardiac standstill of 8.2 seconds (fig. 7 *A*). Fifteen minutes after the subcutaneous injection of 1.2 cc. of epinephrine hydrochloride, 1 : 1,000, pressure on the carotid sinus resulted in an idioventricular rhythm with a rate of 40 (fig. 7*B*). Thirty-five minutes after the injection of the drug a

4. Hering, H. E.: Ueber die unmittelbare Wirkung des Accellerans und Vagus auf automatisch-schlagende Abschnitte des Säugetierherzen, Arch. f. d. ges. Physiol. **108**:281, 1905.

5. Cullis, W. E., and Tribe, E. M.: Distribution of Nerves in the Heart, J. Physiol. **46**:141, 1913.

similar response was obtained with a somewhat more rapid ventricular rate. Fifty-five minutes after the injection of epinephrine hydrochloride, pressure on the right carotid sinus again induced a long cardiac arrest, lasting 9.5 seconds (fig. 7 *D*). From this experiment it appeared that the effect of epinephrine passes off between thirty-five and fifty-five minutes after subcutaneous injection.

Luckhardt and Koppanyi [6] demonstrated in dogs that massage of the site of subcutaneously injected epinephrine hydrochloride may produce a pressor effect many hours after the injection. In the present experiment, the epinephrine was injected without massage of the area

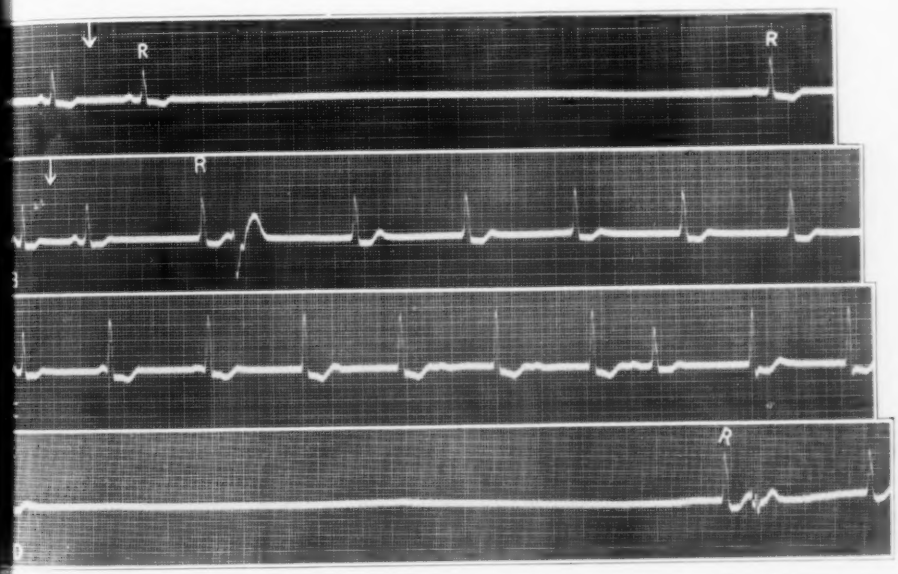

Fig. 7 (patient H. B.).—The duration of the effect of epinephrine. *A*, cardiac standstill of 8.7 seconds after pressure on the right carotid sinus (at arrow); *B*, ventricular rhythm on right carotid pressure, fifteen minutes after the administration of epinephrine. *C*, ventricular rhythm on right carotid compression thirty-five minutes after epinephrine; *D*, cardiac standstill of 9.5 seconds induced by right carotid pressure fifty-five minutes after epinephrine.

of injection. After the effect of the epinephrine had passed off, the site of the injection was actively massaged. Ten minutes after this procedure, pressure on the carotid sinus again elicited a ventricular rhythm similar to that following the injection of epinephrine. Twenty minutes after the massage of the epinephrinized area, a similar effect

6. Luckhardt, A. B., and Koppanyi, T.: Studies on the Hemodynamic Action of Subcutaneously Injected Epinephrine, Am. J. Physiol. **81**:436, 1927.

was obtained (fig. 8). Further studies are in progress concerning the duration of the effect of epinephrine and the renewal of this effect by massage. From this experiment, however, it appears that subcutaneously injected epinephrine remains active, and that there is a return of the cardiac effect after massage of the site of injection.

Ephedrine.—Ephedrine was used because of the similarity of many of its effects to those of epinephrine, and because it is frequently employed as a substitute for this drug. The effect of ephedrine was studied on two occasions on the subject H. B. In the first experiment, ephedrine sulphate was administered by mouth for four days in doses of 50 mg. four times a day. In addition 100 mg. of ephedrine hydrochloride was given subcutaneously one hour before the record was taken. Pressure on the right carotid sinus induced a cardiac standstill of 8.8 seconds (fig. 9). The reaction differed in no way from the usual

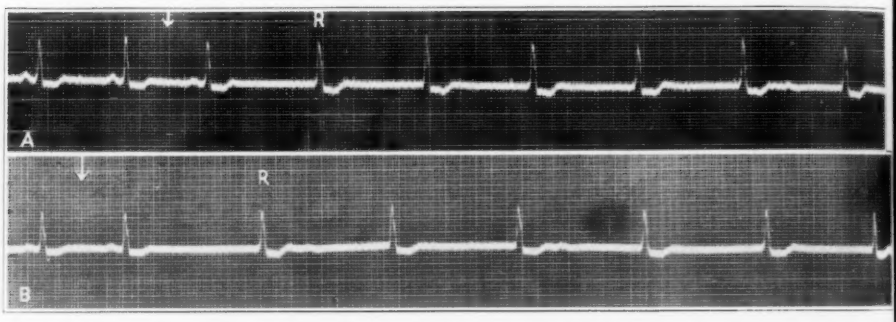

Fig. 8 (patient H. B.).—Massage of the epinephrinized area one hour after subcutaneous injection. *A*, ten minutes after massage, ventricular rhythm rate 43 on right carotid pressure (at arrow). *B*, twenty minutes after massage, ventricular rhythm rate 38 on right carotid pressure (at arrow).

control record. After an interval of three weeks, the experiment was repeated after the subcutaneous injection of 100 mg. of ephedrine hydrochloride, with a similar result. It was apparent that in this patient ephedrine had no effect in increasing the ventricular excitability such as was clearly demonstrated with epinephrine. Certain observations suggest that ephedrine acts differently on the heart than does epinephrine. Gradinesco [7] found that epinephrine is able to restore the beat of the frog's heart which has been arrested by perfusion with ephedrine. Bain [8] perfused the hearts of crabs, and found that epinephrine in 1:50,000

7. Gradinesco, A.: Différence d'action entre l'éphédrine et l'adrénaline, Compt. rend. Soc. de biol. **96**:1027, 1927.

8. Bain, W. A.: Action of Adrenaline and of Certain Drugs on the Isolated Crustacean Heart, Quart. J. Exper. Physiol. **19**:297, 1929.

dilution caused a marked increase in the rate and tone of the heart, while ephedrine had no effect. La Barre [9] showed that ephedrine does not lead to ventricular fibrillation in cats under chloroform anesthesia, in which respect it differs from epinephrine. Wilson, Pilcher and Harrison [10] noted in dogs that both epinephrine and ephedrine usually increase the cardiac output, but that while epinephrine increases the heart rate, ephedrine has the opposite effect. The effect on the human heart has been studied with variable results.[11] A slowing of the heart has been observed most frequently, but acceleration or absence of effect has also been noted. There are several clinical reports which suggest that ephedrine may be substituted for epinephrine in the treatment of the syncopal attacks of heart block. Miller [11b] reported an increase in auricular and ventricular rates following subcutaneous injections of ephedrine. Fahr,[12] Hollingsworth,[13] Stecher [14] and Wood [15] reported favorable results in the prevention of the Adams-Stokes seizures by the oral administration of the drug.

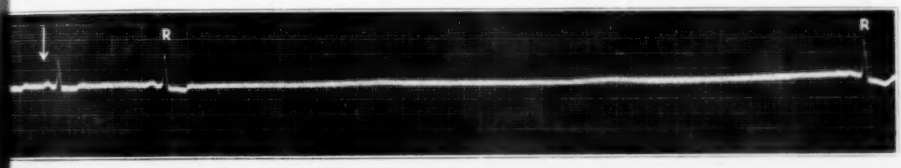

Fig. 9 (patient H. B.).—Effect of ephedrine. Right carotid sinus pressure (at arrow) induced a cardiac standstill of 8.8 seconds after the oral administration of 200 mg. and 100 mg. subcutaneously daily for four days.

9. La Barre, J.: Existe-t-il une syncope éphédrino-chloroformique, Compt. rend. Soc. de biol. **98**:863, 1928.

10. Wilson, C. P.; Pilcher, C., and Harrison, T. R.: The Effect of Drugs on Cardiac Output; Effect of Ephedrine on Minute Cardiac Output of Normal Dogs, Arch. Int. Med. **41**:622 (May) 1928.

11. (*a*) Chen, K. K., and Schmidt, C. F.: The Action of Ephedrine, the Active Principle of the Chinese Drug, Ma Huang, J. Pharmacol. & Exper. Therap. **24**:339, 1924. (*b*) Miller, T. G.: A Consideration of the Clinical Value of Ephedrine, Am. J. M. Sc. **170**:157, 1925. (*c*) Rowntree, L. G., and Brown, G. E.: Ephedrine Therapy in Addison's Disease, Endocrinology **10**:301, 1926. (*d*) Rudolph, R. D., and Graham, J. D.: Notes on Sulphate of Ephedrine, Am. J. M. Sc. **173**:399, 1927. (*e*) Middleton, W. S., and Chen, K. K.: Ephedrine, a Clinical Study, Arch. Int. Med. **39**:385 (March) 1927.

12. Fahr, George: Personal communication.

13. Hollingsworth, M.: Ephedrine in Adams-Stokes Syndrome, California & West. Med. **26**:802, 1927.

14. Stecher, R. M.: A Note on Adams-Stokes Disease Treated with Ephedrine, Am. Heart J. **3**:567, 1928.

15. Wood, J. E., Jr.: Ephedrine in Adams-Stokes Syndrome, J. A. M. A. **98**:1364 (April 16) 1932.

There was no evidence, however, in the present study that ephedrine increased the rhythmic property of the ventricular muscle sufficiently to initiate a ventricular rhythm. It is realized that no definite conclusions are justifiable, since the observations are limited to a single subject, and since it has already been noted that there is some variability

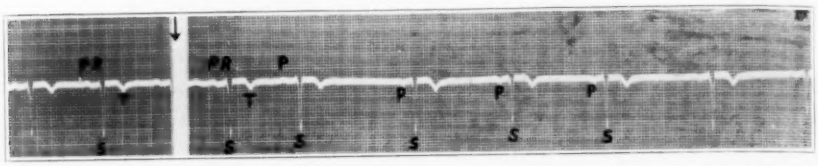

Fig. 10 (patient H. B.).—Lead 3, the effect of the administration of barium chloride, 200 mg. daily by mouth for four days. After right carotid sinus pressure (at arrow) there was a displacement of the pace-maker and a slowing of the heart from 60 to 40 beats a minute.

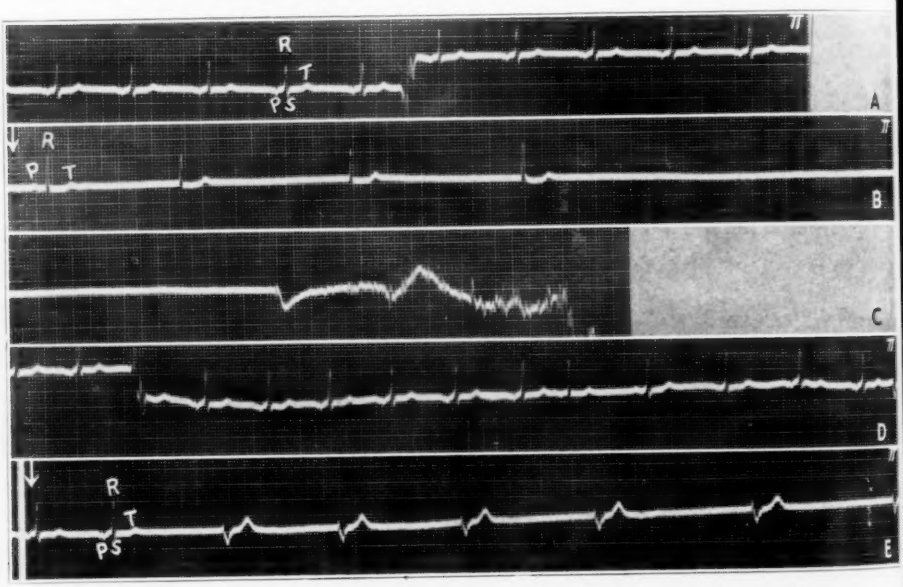

Fig. 11 (patient J. M.).—Effect of barium chloride, 250 mg. a day for three days. *A*, before carotid sinus pressure. *B* and *C* are a continuous record, showing a cardiac arrest of 11.6 seconds after right carotid sinus compression (at arrow). *D*, after the administration of barium chloride without carotid pressure. *E*, right carotid compression (at arrow) after barium chloride showing the development of a slow idioventricular rhythm.

in the effect of ephedrine on the human heart. A study of a larger group of subjects is in progress and will be reported on later. It is

significant, however, that ephedrine failed to have any effect in a person who responded readily to epinephrine.

Barium Chloride.—The effect of barium chloride was studied in two subjects. In the subject H. B., the drug was administered in doses of 50 mg. four times a day. Figure 10 demonstrates that the prolonged cardiac standstill following pressure on the carotid sinus was abolished. The heart rate was slowed from 60 to 40 beats a minute, and the P wave became inverted, indicating the development of a new pacemaker in the auricle. In the second subject, J. M., barium chloride was administered in doses of 250 mg. daily for three days. The strips *B* and *C* in figure 11 form a continuous record showing the effect of pressure on the right carotid sinus prior to the administration of the drug. After a slowing of the heart, there was a period of cardiac standstill of 11.6 seconds, which terminated in a typical Adams-Stokes seizure. The oscillations that appear at the end of the string in strip *C* are due to convulsive movements of the patient's extremities. Figure 11 *E* is a repetition of carotid sinus pressure after the administration of the barium chloride. A series of aberrant ventricular complexes appear indicating the development of an idioventricular rhythm, the rate varying from 30 to 40 beats a minute.

Various experimental studies indicate that barium chloride increases the irritability curve of the ventricles when given in sufficiently large doses. Rothberger and Winterberg [3] observed that after intravenous injection of from 5 to 10 mg. of barium chloride, the heart cannot be arrested by simultaneous stimulation of the sympathetic and vagus nerves, as is the case in the normal heart. With small doses of barium chloride, ectopic ventricular rhythms could regularly be produced by stimulation of the sympathetic nerves. With larger doses, various types of ventricular rhythms occurred spontaneously to the point of ventricular fibrillation. The auricles were affected to a lesser degree than the ventricles. Von Egmond [16] studied the effects of various drugs in experimental heart block. He demonstrated that the ability of the ventricles to initiate rhythms was distinctly increased by barium chloride. After repeated injections of the drug, ventricular fibrillation usually followed. Many patients with clinical cases of heart block have been treated with barium chloride. It has been observed that the drug exerted a beneficial effect in some cases, while in others it apparently was of no value. This treatment was first used by Wilson and Hermann [17] at the suggestion of Dr. S. A. Levine. In this case, there was no effect on the frequency of the Adams-Stokes seizures. Cohn and

16. von Egmond, A. A. J.: Ueber die Wirkung einiger Arzneimittel beim volständigen Herzblock, Arch. f. d. ges. Physiol. **154**:39, 1913.

17. Wilson, F. N., and Hermann, G. R.: Some Unusual Disturbances of the Mechanism of the Heart Beat, Arch. Int. Med. **31**:923 (June) 1923.

Levine,[18] however, have reported beneficial effects from the use of this drug. Parsonnet and Hyman [19] found barium chloride of no value in the treatment of eight patients with heart block. It appears from the present study that barium chloride may in some instances affect the auricles and have little influence on the ventricular muscle, as in the subject H. B. Such an effect would be of no benefit in complete heart block. The subject J. M., however, offers a clear demonstration that barium chloride can increase the ability of the ventricles to initiate a rhythm and thus prevent a cardiac standstill. Following this experiment, the patient H. B. received a subcutaneous injection of epinephrine hydrochloride, 1 : 1,000. Fifteen minutes later, pressure on the right carotid sinus elicited an idioventricular rhythm similar to that induced in the previous experiments with epinephrine. This indicates that the ventricular muscle at this time was susceptible to the initiation of a rhythm if a sufficiently active drug was introduced.

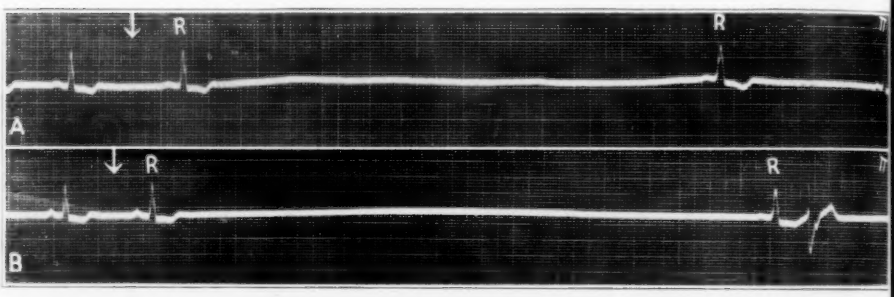

Fig. 12 (patient H. B.).—*A*, cardiac standstill of seven seconds after pressure on the right carotid sinus. *B*, repetition of the pressure twenty minutes after the intravenous injection of 15 cc. of 10 per cent calcium gluconate, with a cardiac arrest of 8 seconds.

Calcium Gluconate.—The effect of calcium gluconate was studied in the subject H. B. on two occasions. Figure 12 shows the effect of an intravenous injection of 15 cc. of a 10 per cent solution. It was apparent from this experiment that the administration of calcium did not raise the rhythmicity of the ventricles sufficiently to initiate a ventricular rhythm during the period of cardiac standstill. Calcium gluconate was then given by mouth in doses of 4 Gm. four times a day for a week. A repetition of the pressure on the carotid sinus again demonstrated that the drug was ineffective. Rothberger and Winterberg [5]

18. Cohn, A. E., and Levine, S. A.: The Beneficial Effects of Barium Chloride on Adams-Stokes Disease, Arch. Int. Med. **36**:1 (July) 1925.

19. Parsonnet, A. E., and Hyman, A. S.: Barium Chloride in Stokes-Adams Syndrome of Complete Heart Block, Am. J. M. Sc. **180**:356, 1930.

concluded that the action of calcium on the rhythmic property of the ventricles was similar to that of barium, but that larger doses were necessary. They noted, however, that with calcium, stimulation of the vagus without stimulation of the accelerators caused a longer cardiac standstill than before the administration of the calcium. These observers consider that the action of barium and calcium is to cause the impulse-initiating mechanism in the ventricles to be more favorably influenced by stimulation of the accelerators. It would seem that the failure of barium and calcium to affect the ventricles in the patient H. B. might be explained by the presence of a low tone of the accelerators. If the response to epinephrine is to be considered as an indication of the degree of accelerator activity, the minimal reaction in this patient supports such a conception. It is also possible that a low tone of the accelerators may explain the cases in which complete heart block was unsuccessfully treated with barium chloride.

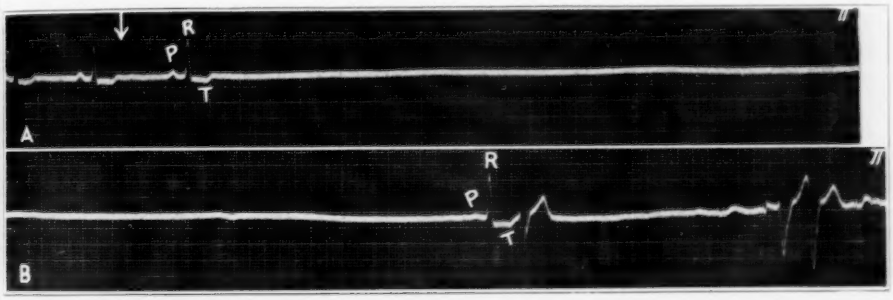

Fig. 13 (patient H. B.).—Effect of digitalis, 3 grains (0.195 Gm.) daily for a week. *A* and *B* form a continuous record showing cardiac standstill of 15.4 seconds after right carotid sinus pressure (at arrow).

Digitalis.—The patient H. B. received 0.2 Gm. of the powdered leaf daily for seven days before the first observations were made. It should be repeated here that in the control studies the longest period of cardiac standstill induced was 9 seconds, and on no occasion was there a period of cardiac arrest of sufficient duration to result in convulsions or syncope. Figure 13 shows the reaction to pressure on the right carotid sinus after the administration of 1.4 Gm. of digitalis in a week. The duration of the cardiac standstill is 15.4 seconds, at which time a typical Adams-Stokes syncope occurred. During the following two weeks, the powdered leaf was administered in doses of 0.12 Gm. a day. During this period a number of observations were made, and the period of cardiac standstill was consistently prolonged as compared with the control records. There was no evidence of idioventricular beats during the period of cardiac arrest in any of the records. It is clear that following

the administration of digitalis there is an exaggeration of the cardiac inhibition induced by pressure on the carotid sinus. The prolongation of the period of cardiac arrest may be explained as a summation of two similar effects, a reflex stimulation of the vagus by the carotid pressure and a stimulation of the vagus by digitalis. Wenckebach [20] stated that digitalis increases the effect of vagus stimulation on the heart. Hering [2] noted in dogs that digitalis intensified the cardiac portion of the carotid sinus reflex. The absence of any tendency to ectopic rhythm may be explained by incomplete digitalization. Rothberger and Winterberg [21] found that strophanthin had a definite influence on ventricular rhythmicity only in toxic doses. Robinson and Wilson [22] observed that while 25 per cent of a fatal dose produced alterations in the T wave and 50 per cent a definite change in the P-R interval, ectopic beats were not elicited until 75 per cent of the lethal dose was used. Gold and his

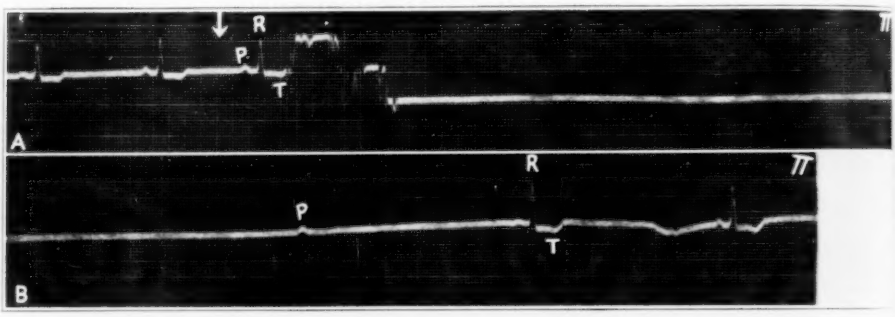

Fig. 14 (patient H. B).—*A* and *B* form a continuous record showing effect of right carotid sinus pressure (at arrow) after administration of 0.7 Gm. of caffeine sodio-benzoate intravenously, with a cardiac arrest of 14.4 seconds. The patient was partially digitalized at the time of this experiment.

associates,[23] however, noted that prolongation of the P-R interval and appearance of ectopic beats occurred in approximately the same dosage in unanesthetized cats. From the present observation it appears that digitalis may distinctly increase the effect of vagus stimulation on the heart in a dosage below that which will induce ectopic ventricular beats.

20. Wenckebach, K. F.: The Effects of Digitalis on the Human Heart, Brit. M. J. **2**:1600, 1910.

21. Rothberger, C. J., and Winterberg, H.: Ueber die Einfluss von Strophanthin auf die Reizbildungsfähigkeit der automatischen Zentren des Herzens, Arch. f. d. ges. Physiol. **150**:217, 1913.

22. Robinson, G. C., and Wilson, F. N.: A Quantitative Study of the Effects of Digitalis on the Heart of the Cat, J. Pharmacol. & Exper. Therap. **10**:491, 1918.

23. Gold, H.; Hitzig, W.; Gelfand, B., and Glassman, H.: A Qualitative Comparison of Various Digitalis Bodies, Am. Heart J. **6**:237, 1930.

The effect of atropine sulphate was observed when the patient was partially digitalized. A cardiac arrest of 15 seconds induced by right carotid sinus pressure was completely abolished by the subcutaneous injection of 2 mg. of atropine sulphate.

Caffeine.—The effect of the administration of caffeine is illustrated in figure 14. The subject was partially digitalized at the time of this experiment, and a cardiac arrest of from 14 to 16 seconds could be easily obtained. Electrocardiograms were taken at various intervals following the administration of the drug. Figure 14 is a typical record taken ten minutes after the intravenous injection of 0.7 Gm. of caffeine sodio-benzoate. Pressure on the right carotid sinus elicited a ventricular standstill of 14.4 seconds interrupted by only one auricular contraction. There is some difference of opinion as to the effect of caffeine on the rhythmic function of the heart muscle. Von Egmond [16] observed in experimental heart block that caffeine caused a transient increase in the rate of ventricular contractions. He obtained this effect, however, only with amounts of the drug far above the ordinary therapeutic dose. Sollmann [24] stated that in experimental heart block caffeine given experimentally in moderate doses increases the rate of the heart, and that large doses may produce ventricular extrasystoles and tachycardia. According to Hirschfelder,[25] however, caffeine has no effect on the duration of ventricular stoppage, as it has been used without effect in cases of Adams-Stokes syncope. The results of this experiment indicate that caffeine in therapeutic doses does not increase cardiac rhythmicity sufficiently for the development of new centers of impulse initiation when the heart is deprived of its normal pacemaker.

COMMENT

There have been many studies concerned with the effect of drugs on the rhythmic property of the heart muscle. This problem is of practical importance since sudden cardiac standstill usually occurs because the heart for a time has lost the mechanism for initiating the stimulus required for its activity. This is frequently the condition underlying the cardiac arrest under anesthesia, in shock, in asphyxia of the new-born or of premature infants and in the ventricular asystole of complete heart block. Previous observations have consisted chiefly of studies in experimental animals both on the normally beating heart and on experimental heart block. The studies on the human heart include reports on the effect of drugs in the prevention of the syncopal

24. Sollmann, T.: A Manual of Pharmacology, ed. 4, Philadelphia, W. B. Saunders Company, 1932, p. 280.

25. Hirschfelder, A. D.: Diseases of the Heart and Aorta, ed. 3, Philadelphia, J. B. Lippincott Company, 1918, p. 587.

attacks of heart block and on the methods of resuscitation of the stopped heart by intracardiac therapy. From the various observations there has been no general agreement as to the efficiency of drugs in the prevention and treatment of cardiac standstill. The method of cardiac arrest induced by pressure on the carotid sinus permits a direct and well controlled study of the action of the drugs on the rhythmic property of the human heart muscle. It is recognized that the comparatively small number of observations does not permit a final conclusion as to the exact efficiency of the various drugs used. The fact that epinephrine, when repeatedly used in one subject and in four others, consistently abolished the cardiac standstill by initiating an idioventricular rhythm strongly indicates that this drug exerts a powerful effect on the rhythmic property of the ventricular muscle. The study of a larger group of suitable subjects is in progress in order to evaluate more accurately the efficiency of various drugs and also to bring out certain features of their action, such as the duration of the effect and the influence of the mode of administration.

SUMMARY

1. The prolonged cardiac standstill induced by pressure on the carotid sinus was utilized as the basis for the study of the effect of drugs on the rhythmic function of the human heart.

2. The exaggerated carotid sinus reflex in man could be abolished by atropine.

3. Epinephrine had a powerful effect on the impulse-initiating mechanism of the ventricles and consistently prevented cardiac standstill by the induction of an idioventricular rhythm.

4. The stimulation of cardiac rhythmicity by the administration of epinephrine passed off within an hour after a subcutaneous injection. The effect returned after massage of the site of injection.

5. Ephedrine had no effect in a patient who repeatedly responded to epinephrine with initiation of a ventricular rhythm.

6. Barium chloride abolished cardiac arrest in one case by the formation of a new center in the auricles and in another instance by the development of an idioventricular rhythm.

7. Calcium gluconate had no influence on the cardiac standstill.

8. Digitalis definitely prolonged the period of cardiac standstill induced by pressure on the carotid sinus. This effect was abolished by atropine.

9. Caffeine in a therapeutic dose had no effect on the duration of the cardiac arrest.

HYPERPLASTIC SCLEROSIS OF THE PULMONARY ARTERY AND ARTERIOLES

REPORT OF A CASE WITH DISCUSSION OF THE PATHOGENESIS

MARTIN J. SOKOLOFF, M.D
Instructor in Medicine
AND
HAROLD L. STEWART, M.D.
Demonstrator in Pathology
PHILADELPHIA

Sclerosis of the pulmonary artery and arterioles associated with Ayerza's syndrome occurs secondary to a variety of diseases, congenital and acquired, of the heart, lungs, pericardium, pleura and blood vessels (Miller[1]). Primary sclerosis developing independently of these conditions is much less frequent. The majority of the latter cases are due to syphilis (Rogers,[2] Warthin,[3] Arrillaga,[4] Elizalda,[5] Hare and Ross,[6] Thomas,[7] Bruce and co-workers,[8] Cheney,[9] Weber and Bode[10] and Konstam and Turnbull[11]); a few to rheumatic fever (Paul[12]). In a smaller group the lesion is hyperplastic and noninflammatory and the etiology obscure (Rosenthal,[13] Bacon and Apfelbach[14]).

This study was aided by a grant from the Martin Research Fund.

From the Department of Diseases of the Chest and the Pathological Laboratories of the Jefferson Medical College and Hospital.

1. Miller, H. R.: M. Clin. North America **9**:673, 1925.

2. Rogers, L.: Quart. J. Med. **2**:1, 1908.

3. Warthin, A. S., in Contributions to Medical and Biological Research, New York, Paul B. Hoeber, Inc., 1919, vol. 2, p. 1042.

4. Arrillaga, F. C.: Monograph on Cardiacos Negros, Buenos Aires, 1925.

5. Elizalda, P., quoted by Escudero, P.: Arch. d. mal. du cœur **19**:439, 1926.

6. Hare, D. C., and Ross, J. M.: Lancet **2**:806, 1929.

7. Thomas, Marcel: Thèse de Paris, 1929, no. 474.

8. Bruce, J. D.; Wilson, F. N.; Hickey, P. M.; Coller, F. A., and Warthin, A. S.: Ann. Clin. Med. **5**:9, 1926.

9. Cheney, G.: Am. J. M. Sc. **174**:34, 1927.

10. Weber, F. P.: Brit. M. J. **2**:658, 1920; Polycythemia, Erythrocytosis and Erythremia, London, H. K. Lewis & Co., Ltd., 1921. Weber, F. P., and Bode, O. B.: Polycythemia, Erythrocytosis and Erythremia, London, H. K. Lewis & Co., Ltd., 1929.

11. Konstam, G. L. S., and Turnbull, H. M.: Lancet **2**:756, 1929.

12. Paul, J. R.: Lesions in the Pulmonary Artery in Rheumatism, Arch. Path. **3**:354 (Feb.) 1927.

13. Rosenthal, S. R.: Sclerosis of the Pulmonary Artery and Arterioles, Arch. Path. **10**:717 (Nov.) 1930.

14. Bacon, C. M., and Apfelbach, C. W.: Tr. Chicago Path. Soc. **12**:293, 1924-1927.

REPORT OF CASE

G. P., a stevedore, white, aged 48, was first seen in October, 1924, complaining of a cough productive of a small amount of mucus, a feeling of constriction across the upper part of the chest and dyspnea, which had developed over a period of five years. The family history was irrelevant. His wife had had five children, all living and well, and had had no miscarriages. He had typhoid fever in 1906 and influenza and pneumonia in 1918; he denied having had gonorrhea or syphilis.

He was obese, dyspneic and cyanotic. There was no clubbing of the fingers or curving of the nails, and the radial arteries were not thickened. The chest was barrel-shaped, expansion limited and vocal fremitus normal. The percussion note was hyperresonant, and musical râles obscured the breath sounds. The apex beat was not visible or palpable, the area of cardiac dulness was diminished, sounds were distant and regular and there were no murmurs. There was a marked accentuation of the pulmonic second sound. The liver was not enlarged and the spleen was not palpable. Blood pressure was 145 systolic and 98 diastolic.

No tubercle bacilli, Curschmann's spirals or Charcot-Leyden crystals were found in the sputum. The urine contained a faint trace of albumin but no casts. Repeated Wassermann and Kahn tests of the blood were negative. The hemoglobin content was 85 per cent; the erythrocytes ranged between 4,300,000 and 5,200,000; the leukocytes numbered 10,880, of which 66 per cent were polymorphonuclears, 29 per cent lymphocytes and 4 per cent eosinophils. Blood sugar amounted to 116 mg., calcium to 11.5 mg. and phosphorus to 3.6 mg.

On bronchoscopic examination the bronchial mucosa was congested and covered with adherent tenacious mucopurulent material.

Roentgen examination of the chest showed the root markings increased in density. The heart was slightly enlarged to the right, and there was some increase in the shadow in the region of the arch of the pulmonary artery. The left seventh rib showed an old fracture.

Electrocardiographic study on April 21, 1927, showed: cardiac rate, 105 per minute; rhythm regular; conduction function normal; no disturbance of muscle balance, and no indications of myocardial degeneration.

During the period of observation from 1924 until the patient's death, dyspnea, cyanosis and a brassy cough were continuously present. On two occasions death appeared imminent. Early in 1925, paroxysmal dyspneic attacks, simulating asthma, developed; these usually occurred at night, frequently as often as five times a week, and were only occasionally relieved by epinephrine. On testing for susceptibility to proteins a severe reaction was obtained with dog and rabbit hair. Attempts to desensitize the patient resulted in no improvement. His condition remained unchanged until February, 1930, when an acute respiratory infection precipitated a sudden exacerbation accompanied by a small pulmonary hemorrhage. In June, 1931, he became bedfast on account of weakness and headaches, which were constant, severe and greatly aggravated by coughing. The dyspnea became intense and was present even during sleep. Edema appeared, and involved chiefly the chest, abdomen and external genitalia. The cyanosis deepened, causing a decided change in the patient's appearance. Beginning as a ring around the neck at the lower border of the thyroid cartilage, it extended upward over the face and head, and was also marked beneath the finger and toe nails. During sleep and following paroxysms of coughing the face turned black. In July the asthmatic attacks and the feeling of thoracic constriction disappeared. The pain was now localized, constant and aggravated by coughing. In the latter part of November the patient became drowsy; edema and cyanosis increased; the headache and precordial pain disap-

peared. The temperature remained below 99.2 F.; the pulse rate between 92 and 110. Death occurred in stupor on Dec. 15, 1931.

It was apparent that chronic bronchitis, emphysema and bronchial asthma were present. It did not appear that these were enough to cause so severe a grade of cyanosis or such distressing constant dyspnea. The symptoms resembled more those due to increased pressure within the chest. The possibility of a new growth, aneurysm, enlarged bronchial nodes or a persistent thymus was considered. Lack of definite physical signs and negative roentgenographic, bronchoscopic and laboratory evidence eliminated these. With the development of edema and the typical appearance of the "black cardiac" during the last few months of life, it became increasingly evident that the heretofore unexplained symptoms were due to sclerosis of the pulmonary artery.

Postmortem Examination.—This was conducted two hours after death. Edema was generalized and especially marked on the trunk, scrotum and penis. There were deep cyanosis and scattered petechiae of the face and extremities. The peritoneal cavity contained 6,000 cc., the left pleural cavity 800 cc., the right pleural cavity 300 cc. and the pericardium 200 cc. of a thin, clear transparent fluid.

The heart was hypertrophied and dilated, and weighed 530 Gm. The apex was formed by the right ventricle, the wall of which was 10 cm. thick. The columnae carneae and papillary muscles were hypertrophied and flattened. The valve rings were dilated and the endocardium normal. The myocardium, aorta and coronary arteries were normal except that the right coronary was dilated.

Anteriorly both lungs were crepitant, voluminous, dry, light brown, resistant to compression and partially collapsed posteriorly. The bronchi were contracted and thickened. The first portion of the pulmonary artery was dilated, and in its main branches were a few flat, grayish-yellow, firm plaques, which became more numerous with each succeeding branch.

The spleen was enlarged, congested and fibrotic.

The liver was dark red, shrunken, firm, tough and slightly nodular, and cut with increased resistance.

Both kidneys were congested. The suprarenals were swollen, bright yellow and well preserved.

The stomach and upper portion of the small intestine were congested, the mucosa was necrotic and the lumen contained coffee-ground material.

The lymph nodes about the aorta were dark red, swollen and soft.

The bone marrow in the ribs, vertebrae and sternum was bright red. There was an osseous irregularity of the seventh left rib at the sternal border, which had the appearance of an old fracture and caused compression of the intercostal tissues.

The anatomic diagnosis was: sclerosis of the pulmonary artery; hypertrophy and dilatation of the right side of the heart; emphysema of the lungs; passive congestion of the liver, spleen, lymph nodes, kidneys, suprarenals, stomach and intestine; petechial hemorrhages of the skin; anasarca, and hyperplasia of the bone marrow.

Microscopic Examination.—Sections were fixed in Zenker's fluid and a diluted solution of formaldehyde, U.S.P. (1:10), blocked in paraffin and stained with hematoxylin-eosin, Mallory's and van Gieson's connective tissue stains, Verhoeff's elastic tissue stain, Levaditi's method for demonstrating spirochetes in sections, and Gram's stain for bacteria in tissues.

Pulmonary Artery: The adventitia was normal. The wall of the vessel was generally widened by an increase in the size and number of elastic fibers. The intima showed mild generalized hyperplastic thickening, amounting in places to flat, slightly elevated plaques, which consisted of cellular connective tissue and frayed

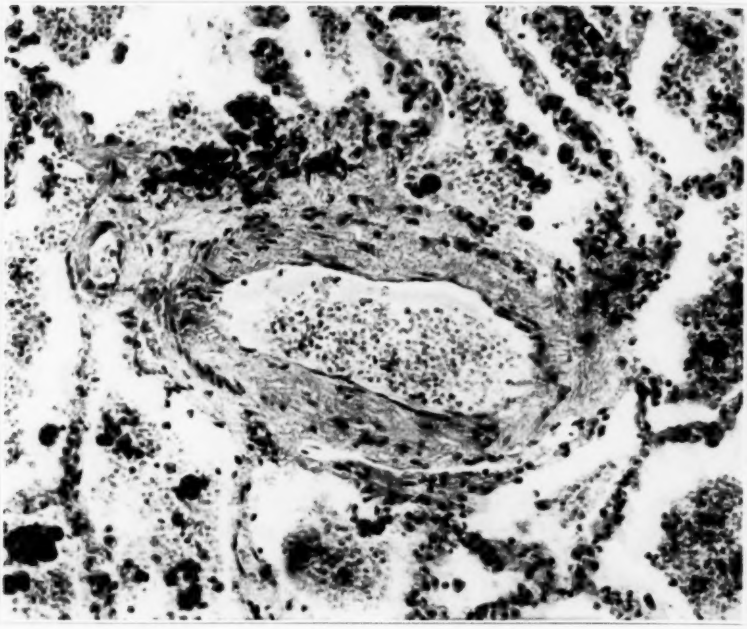

Fig. 1.—Lung: an artery and to the left of it a small arteriole showing sclerotic process. There are congestion of capillaries in the septums, hemorrhage and "heart failure" cells in the alveoli; × 170.

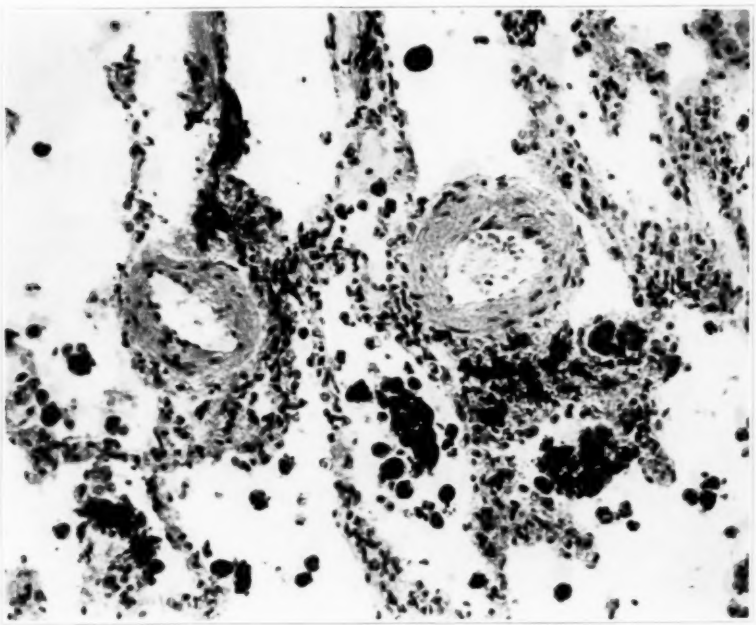

Fig. 2.—Lung: two small arteries with thickened walls. Many "heart failure" cells are present in the alveoli; × 190.

elastic fibers. As the artery branched these changes gradually became more marked and differed in character. The intrapulmonary branches measuring from about 0.4 to 1 mm. (figs. 1 and 2) were greatly thickened and their lumens correspondingly narrowed. The thickening was chiefly the result of changes in the media and intima. The medial changes were an increase in muscle cells, elastic fibers and connective tissue. The intimal changes were a hyperplastic increase in connective tissue, hypertrophy, longitudinal splitting and fraying of the internal elastic lamina (fig. 3). Variations of this consisted in great intimal thickening, atrophy of the adventitia and media and fusion of the internal and external laminae. Occa-

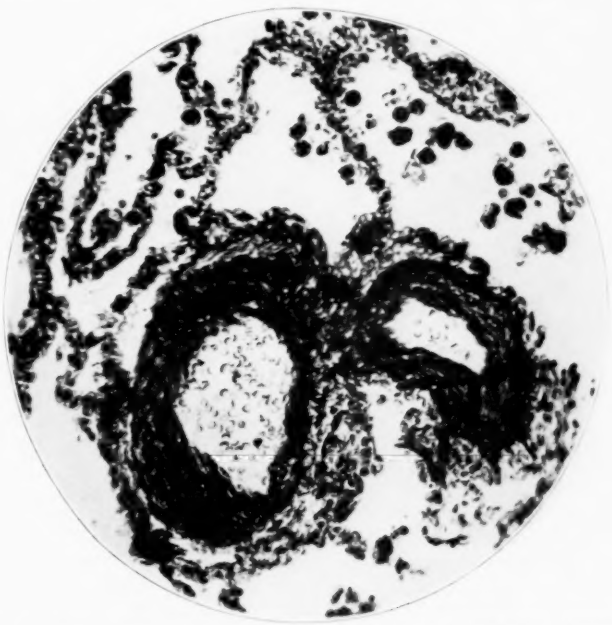

Fig. 3.—Lung: two small arteries in which there is splitting, fraying and reduplication of the elastica. Verhoeff's elastic tissue stain; × 170.

sionally obstruction to the lumen resulted from nodular hypertrophy of the media. These changes became more accentuated with the branching of the arteries; those about 0.2 mm. in diameter and smaller were completely occluded and all the rest greatly diminished. The process was much simpler and consisted of a subendothelial fibrosis in which elastic fibers were not so numerous or so large as in the medium-sized vessels (fig. 1). The media was unchanged or but slightly atrophied. In none of the arteries were there any fresh thrombi. The vasa vasorum in all were dilated but otherwise unchanged. In none of them were there any round cell infiltrations. An occasional vacuolated space was noted in the media. The walls of the pulmonary capillaries were distinctly thickened. The pulmonary veins were normal except for one or two instances, in which thickening was slight. No bacteria were demonstrated.

Lungs: Great numbers of polyblasts loaded with golden yellow and brownish pigment granules were present in the alveolar spaces. There was no edema, but in scattered patches gross hemorrhage was present (figs. 1 and 2). Areas of partial collapse and emphysema were encountered, but neither was a striking feature. The alveolar walls were thickened by hyperemic capillaries and an appreciable increase of cellular and hyalinized connective tissue. They contained what small quantities of carbon deposit were present. In many the elastic fibers were apparently increased, but serial sections showed that this was mainly an artefact, most of the fibers belonging to the walls of arteries.

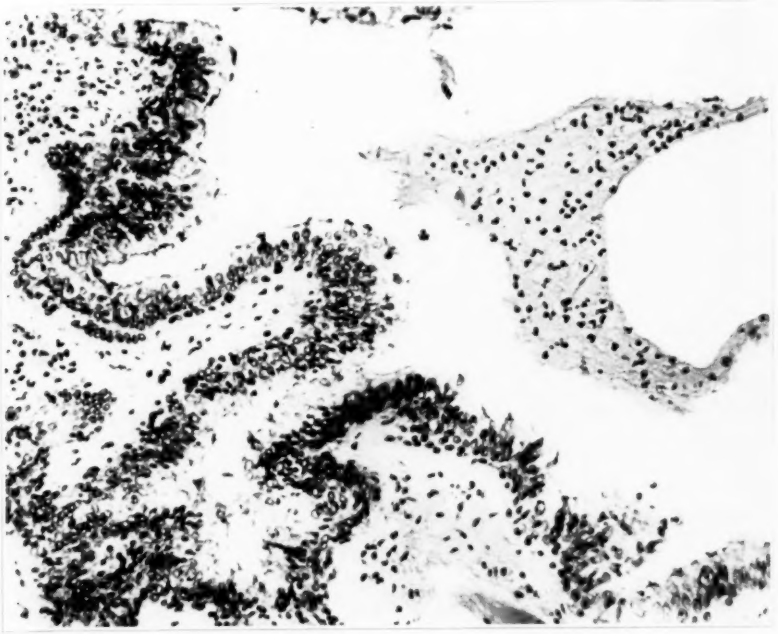

Fig. 4.—Bronchus. In the lumen there is a small amount of mucus in which eosinophils and neutrophils are caught. Folding of the mucosa and proliferation of bronchial epithelium can be seen. There is a slight infiltration of cells in the bronchial wall; × 125.

The fibrous and muscular coats of the bronchi were slightly thickened. Their walls were sparsely infiltrated by eosinophilic and neutrophilic granulocytes. The vessels were hyperemic, but their walls were unchanged. The mucosa was thrown into folds and the lining cells proliferated to form in places from five to eight layers (fig. 4). The lumens of many bronchi were narrowed and contained a small amount of stringy mucus, in the meshes of which were entangled desquamated epithelial cells, eosinophilic and neutrophilic granulocytes.

The arteries of the heart, kidney, spleen, liver and suprarenals were normal. In the liver about the portal radicals there was an active fibrosis with lymphocytes

and proliferating bile ducts. It was of the nature of portal cirrhosis, but was not extensive enough to be so classed.

In the suprarenals the cells of the zona glomerulosa and medulla stained darkly. They were remarkably well preserved. Those of the zona fasciculata were more foamy than usual, owing to a large amount of lipoid.

In other respects the microscopic examination confirmed the gross findings.

COMMENT

The patient was under close clinical observation for seven years. As an etiologic factor syphilis was as well ruled out as possible. The history was not significant. The patient had no scars on the penis, and he had never had antisyphilitic treatment. The Wassermann and Kahn reactions of the blood were negative. The patient's wife had had five children and no miscarriages. All the children were living and healthy, and none showed any stigma of hereditary syphilis. There were no suggestive clinical manifestations, and roentgen studies of the patient's skeleton revealed no syphilitic lesions. After death no gross or microscopic evidences of the disease were found in the tissues. No spironemas could be demonstrated, although diligently searched for. In the sections of the pulmonary arteries and arterioles there were no newly formed capillaries, round cell infiltrations in the adventitia and media or proliferative endarteritis of the vasa vasorum, characteristic of syphilitic arteritis.

Rosenthal's [13] cases of sclerosis of the pulmonary artery and arterioles were associated with constant aspiration of particulate matter (sand, iron) or fumes (naphtha, benzene), which he believed led to spasm and necrosis of capillary endothelium. Bacon and Apfelbach [14] regarded influenza as playing an important etiologic rôle. They reviewed some studies made on influenza during the acute attack in which necrosis of the capillary endothelium was observed. It is interesting that in our case symptoms appeared one year after an attack of influenzal pneumonia. McCann and Stephens [15] suggested rheumatic fever, but the changes in the arteries are not similar to those described for human beings (Pappenheimer and Von Glahn [16]) or for animals (Moon and Stewart [17]).

The present case suggests one of two other pathogenic factors. The first is endocrine. Over a long period of time this patient received injections of epinephrine hydrochloride. At autopsy the suprarenal cells were remarkably well preserved and were found to have a high

15. McCann, William S., and Stephens, D. J.: Tr. Am. Climat. & Clin. A. **47**:3, 1931.

16. Pappenheimer, A. M., and Von Glahn, W. C.: Am. J. Path. **2**:15, 1926.

17. Moon, V. H., and Stewart, H. L.: Experimental Rheumatic Lesions in Dogs and in Rabbits, Arch. Path. **11**:190 (Feb.) 1931.

content of lipoid (Cheney [9]). It has been shown that similar hyperadrenalization of animals is followed by analogous lesions (Shaw,[18] Pearce [19] and Palenttini [20]). Its effect is probably manifested by increasing resistance to blood flow, which Moschowitz [21] believes is of such great importance in causing arteriosclerosis.

The second factor is neurologic. There was an irregularity of the seventh left rib at the costosternal junction which diminished the intercostal space and pressed on the soft tissues. The tremendous effect of such a slight and apparently insignificant lesion is well exemplified by the occasional occurrence of paralytic ileus following fracture of the ribs (Christopher [22]). There have been many observations, both clinical and experimental, that sclerosis of the arteries results when nerves are injured or stimulated (Stapford,[23] Todd,[24] Schaeffer,[25] Shaw). To the case under consideration Manouelian's [26] findings are particularly applicable. He incised the pericardium of an animal and removed a nerve filament going to the pulmonary artery. At autopsy, sixty-five days later, a sclerosed plaque was found in the part of the vessel that was deprived of its nerve supply.

Lesions of the systemic circulation similar to this one have been described by Evans,[27] Fishberg [28] and Kernohan, Anderson and Keith.[29] They occur in the kidney, less frequently in other organs, and consist of a diffuse hyperplastic sclerosis, mainly of the arterioles, associated with hypertrophy of the left side of the heart and a high blood pressure. The etiology is unknown, although it has been considered to be involutionary. Jores [30] thought it the result of stress. We regard the present case as a pure example of this disease entity with the manifestation of the pathology and pathologic physiology limited to the lungs, the lesser circulation and the right side of the heart, and suggest that it be classified as sclerosis of the arteries.

18. Shaw, R. Cunliff: Quart. J. Med. **19**:203, 1926.
19. Pearce, R. M.: Bull. Johns Hopkins Hosp. **17**:94, 1906.
20. Palenttini, D. B.: Arch. per le sc. med. **43**:63, 1920.
21. Moschowitz, Eli: Am. J. M. Sc. **174**:388, 1927.
22. Christopher, F.: Ann. Surg. **90**:394, 1929.
23. Stapford, J. S. B.: Lancet **1**:465, 1918.
24. Todd, T. W.: J. Nerv. & Ment. Dis. **40**:439, 1913; Anat. Rec. **8**:243, 1914; J. Anat. & Physiol. **47**:250, 1913.
25. Schaeffer, J. P.: Pennsylvania M. J. **34**:786, 1931.
26. Manouelian, Y.: Ann. Inst. Pasteur **27**:14, 1913.
27. Evans, G.: Quart. J. Med. **14**:215, 1920.
28. Fishberg, A. M.: Anatomic Findings in Essential Hypertension, Arch. Int. Med. **35**:650 (May) 1925.
29. Kernohan, J. W.; Anderson, E. W., and Keith, N. M.: The Arterioles in Cases of Hypertension, Arch. Int. Med. **44**:395 (Sept.) 1929.
30. Jores, L.: Wesen und Entwickelung der Arteriosklerose, Munich, J. F. Bergmann, 1903.

There has been a gradual change in the knowledge concerning sclerosis of the pulmonary artery. According to the researches of Yater and Konstam,[31] it was first described by Vieussens in 1706. Subsequent discussion appeared in 1816 (Kreysig), 1826 (Louis), 1828 (Laennec), 1829 (Andral) and 1835 (Bouilland). The modern conception began with the papers of Posselt,[32] Saunders,[33] Giroux,[34] Veale and Coombs,[35] Eppinger and Wagner,[36] Mattirolo,[37] and Gamna,[38] although Romberg[39] (1891) and Aust[40] (1892) roughly constructed the picture. In 1901 Abel Ayerza, in a clinical lecture, described the syndrome of hypertrophy of the right ventricle associated with polycythemia, cyanosis and dyspnea. He gave it the name of "cardiacos negros." The term "Ayerza's disease" was introduced years later and used to designate sclerosis of the pulmonary artery, either primary or secondary (Warthin[3]). Later it was used for those cases due to syphilis (Cheney[9]). In view of the attendant confused nomenclature we suggest that "Ayerza's syndrome" should be limited to designating the complex of symptoms associated with "black cardiacs." It should not be used in the sense of designating any specific pathologic process, whether syphilitic or otherwise.

The association of paroxysmal dyspnea (asthma) with this case is interesting. It did not appear until after the symptoms had been present for six years, and it disappeared six months before death. Its failure, except on occasion, to respond to ephedrine and epinephrine therapy and the negative results from desensitization definitely place this case outside the general run of cases. Morbid changes in the bronchi were similar to those described for mild cases of asthma (Monckeberg,[41] Huber and Koessler[42]). The same changes could be explained on different grounds. Falta[43] and Eppinger and Hess[44] showed that pul-

31. Yater, W. M., and Konstam, G. R.: M. Clin. North America **12**:1689, 1929.
32. Posselt, A.: Ergebn. d. allg. Path. u. path. Anat. **13**:398, 1909; Wien. Arch. f. inn. Med. **11**:357, 1925.
33. Saunders, W. E.: Primary Pulmonary Arteriosclerosis with Hypertrophy of the Right Ventricle, Arch. Int. Med. **3**:257 (April) 1909.
34. Giroux, Leon: Arch. d. mal. du cœur **3**:595, 1910.
35. Veale, P. J., and Coombs, C.: Brit. J. Child. Dis. **12**:72, 1915.
36. Eppinger, H., and Wagner, R.: Arch. f. inn. Med. **1**:83, 1920.
37. Mattirolo, G.: Arch. per le sc. med. **44**:124, 1921.
38. Gamna, C.: Pathologica **13**:207, 1921.
39. Romberg: Deutsches Arch. f. klin. Med. **48**:197, 1891.
40. Aust, C.: München. med. Wchnschr. **39**:689, 1892.
41. Monckeberg, J. G.: Verhandl. d. deutsch. path. Gesellsch. **14**:173, 1909.
42. Huber, H. L., and Koessler, K. K.: The Pathology of Bronchial Asthma, Arch. Int. Med. **30**:689 (Dec.) 1922.
43. Bertelli, Falta and Schwerger: Ztschr. f. klin. Med. **71**:23, 1910.
44. Eppinger, H., and Hess, L.: Vagotonie, Berlin, A. Hirschwald, 1910, p. 60.

monary eosinophilia resulted from vagotonia; Pescatori,[45] that it accompanied any asphyxial phenomenon. Winternitz and co-workers[46] stimulated bronchial epithelial proliferation in animals by the insufflation of acids, and Eppinger and Wagner[36] have demonstrated the rôle of the lung in lactic acid metabolism. Hypertrophy of the bronchi commonly results from overwork. Chronic bronchitis is constantly associated with impaired pulmonary circulation and the liberation of blood pigments (Boyd[47]). It must be considered that the mild and atypical clinical and pathologic evidences of asthma were either concomitant with the pulmonary arteriosclerosis or associated with it in some way other than as an etiologic factor.

Careful examination into the family did not reveal a hereditary factor (Kidd,[48] Clark and co-workers[49]). No infarcts formed (Loubry and Thomas,[50] and McCann and Stephens[15]) despite the grave vascular damage. We agree with Clark that the diffuse dropsy is more an evidence of a toxic or privational metabolic disturbance than of a simple mechanical breakdown. While the erythrocytes as counted numbered only 5,200,000, undoubtedly their number would have been found to be higher (Weber and Bode[10]) if failure of cooperation had not prevented their being counted later in the disease.

CONCLUSIONS

A case of hyperplastic sclerosis of the pulmonary artery and arterioles is reported. The distinguishing features, clinical and pathologic, between this disease and syphilitic sclerosis of the pulmonary artery are discussed. The associated factors of etiologic importance were a prior attack of influenzal pneumonia, increased epinephrine in the circulating blood, stimulation, probably reflexly, of the nerves supplying the pulmonary artery, and asthma.

The term "Ayerza's disease" should not be used synonymously with sclerosis of the pulmonary artery, since the pathologic process may be present for years before the complex of symptoms which Ayerza described make their appearance.

45. Pescatori, F.: Riv. di path. e clin. d. tuberc. **4**:735, 1930.

46. Winternitz, M. C.; Smith, G. H., and McNamara, F. P.: J. Exper. Med. **32**:205, 1920.

47. Boyd, William: Pathology of Internal Diseases, Philadelphia, Lea & Febiger, 1931, p. 137.

48. Kidd, P.: Tr. Clin. Soc., London **37**:192, 1904.

49. Clark, R. C.; Coombs, C. F.; Hatfield, G., and Todd, A. T.: Quart. J. Med. **21**:51, 1928.

50. Loubry, W., and Thomas, M.: Bull. et mém. Soc. méd. d. hôp. de Paris **51**:9, 1927.

PEPTIC ULCERS (GASTRIC, PYLORIC AND DUODENAL)

OCCURRENCE IN GUINEA-PIGS FED ON A DIET DEFICIENT IN VITAMIN C

DAVID T. SMITH, M.D.
AND
M. McCONKEY, M.D.
RAY BROOK, N. Y.

The etiology of peptic ulcer in man is unknown. Heredity, occupation, infections, tobacco, alcohol, worry and trauma of the mucous membrane from hot foods have been suggested as etiologic factors, but are inadequate explanations. The relation of vitamins to tuberculous ulceration of the intestine as demonstrated in our previous studies [1] suggested that peptic ulcer might be due to a deficiency of certain vitamins in the dietary.

HISTORIC REVIEW

The following data also suggest that peptic ulcer may be related to the dietary. The incidence of peptic ulcer varies in different countries: 0.8 per cent in Russia, 1.3 per cent in North America, 5 per cent in England and Germany and 16 per cent in Denmark. A marked increase in the incidence of peptic ulcer occurred in Russia and Germany during the period of partial starvation which followed the World War (from 1914 to 1918).[2] Hutter [3] stated that the peak of incidence of peptic ulcer occurs during the late winter and early spring. This type of ulcer is commonly associated with malnutrition in infants.[4]

Rosenow [5] found peptic ulcers in sheep, cows and calves at the Armour abattoir in Chicago. He was told that "the incidence of ulcer

From the New York State Hospital for Incipient Pulmonary Tuberculosis.

1. (*a*) McConkey, M.: Treatment of Intestinal Tuberculosis with Cod Liver Oil and Tomato Juice, Nat. Tuberc. A. Tr. **25**:105 (May) 1929. (*b*) Smith, D. T., and McConkey, M.: Experimental Intestinal Tuberculosis in the Guinea-Pig Induced by Feeding Tubercle Bacilli to Animals Living on a Diet Deficient in Vitamins, ibid. **25**:627 (May) 1929.

2. Cecil, Russell L.: A Textbook of Medicine, Philadelphia, W. B. Saunders Company, 1930, p. 688.

3. Hutter, K.: Seasonal Variations in Occurrence of Gastric and Duodenal Ulcers, J. A. M. A. **91**:2030 (Dec. 22) 1928.

4. Holt, Luther Emmett: Diseases of Infancy and Childhood, ed. 12, New York, D. Appleton and Company, 1923, p. 337.

5. Rosenow, Edward C.: Etiology of Spontaneous Ulcer of Stomach in Domestic Animals, J. Infect. Dis. **32**:384 (May) 1923.

in the cow and the sheep was highest each year during the latter part of the winter and early spring months and that in their opinion the ulceration was the result of eating dry, coarse foods during these months, since the condition disappeared almost entirely each year during the summer and fall months when the animals were on pasture." Ivy [6] reported that peptic ulcer is rare in healthy dogs. In nine hundred autopsies he found only one ulcer (0.11 per cent). The animal was old and emaciated. On the other hand, as high as 2.5 per cent of peptic ulcers has been reported by Rosenow [5] among animals killed by gas in a dog-pound. Underhill and Mendel [7] found duodenal ulcers in dogs fed a diet of cooked meat, crackers, lard and beans.

Most of the experimental work on deficiency of vitamin C has been confined to guinea-pigs. In 1895, Theobald Smith [8] noted that in guinea-pigs fed a diet of bran and oats a peculiar disease characterized by subcutaneous and submucosal extravasation of blood developed, but in a recent personal communication he said that no true ulceration in the region of the duodenum was noted. Holst and Frölich,[9] in their studies on experimental scurvy (1907), noted the occurrence of peptic ulcer with occasional perforation in some of the guinea-pigs. The diet on which the animals were fed consisted of bread and grains of different types. McCarrison,[10] in 1919, fed nine guinea-pigs a diet of crushed oats and autoclaved milk, and in three he found necrotic ulcers in the stomach. "These changes," he said, "were present in the gastro-intestinal tract of guinea pigs dying in consequence of this dietary, although none of the animals presented the characteristic naked-eye appearances of scurvy. In a clinical sense, then, they may be regarded as prescorbutic." The same investigator also fed four guinea-pigs on a diet of autoclaved rice. At necropsy all the animals showed marked congestion of the duodenum, and one had a well marked ulcer extending to the peritoneal coat. In 1931, McCarrison [11] repeated his experiments on guinea-pigs and obtained data on the various stages of development in duodenal ulcers. He also reported the production of gastric ulcers in

6. Ivy, A. C.: Studies on Gastric Ulcer, Arch. Int. Med. **25**:6 (Jan.) 1920.

7. Underhill, F. P., and Mendel, L. B.: A Dietary Deficiency Canine Disease, Am. J. Physiol. **83**:589, 1928.

8. Smith, Theobald: Investigation of Diseases of Domestic Animals, U. S. Dept. Agric., Bur. Animal Industry, Ann. Rep. 12 and 13, 1895, p. 171.

9. Holst, Axel, and Frölich, Theodor: Experimental Studies Relating to Ship Beri-Beri and Scurvy, J. Hyg. **7**:634, 1907.

10. McCarrison, Robert: Studies in Deficiency Disease, New York, Oxford University Press, 1921, p. 95.

11. McCarrison, Robert: Some Surgical Aspects of Faulty Nutrition, Lancet **1**:1151 (May 23) 1931.

rats fed on a deficient diet. Hess [12] mentioned the occurrence of duodenal ulcers in scorbutic guinea-pigs, but gave no data as to their frequency. Magee, Anderson and McCallum [13] fed guinea-pigs on diets deficient in vitamin C and in minerals. In one series, peptic ulcers, one of which perforated, developed in seven of thirty-two guinea pigs. From each of fifteen additional guinea-pigs one suprarenal gland was removed, and the animals were then given the deficient diet. Peptic ulcers developed in four of them.

Peptic ulcer was not mentioned as a manifestation of scurvy by Jackson and Moore,[14] McCollum and Pitz,[15] Cohen and Mendel [16] and Sherman, LaMer and Campbell,[17] although they all noted the occurrence of intestinal hemorrhage. These observers generally used young guinea-pigs and attempted to produce acute scurvy.

EXPERIMENTS

We noted while studying the effect of deficiency of vitamins in relation to production of intestinal tuberculosis in the guinea-pig [1b] that peptic ulcer was associated with scorbutic lesions. The following experiments were conducted to learn, if possible, the factor or factors responsible for the development of peptic ulcer in the guinea-pig.

The guinea-pigs used in the following experiments were raised in our laboratory. The stock diet consisted of hay, water, cabbage, carrots and a mixture of dry food containing 25 per cent white bread, 25 per cent bran, 24 per cent whole wheat flour, 15 per cent dry skimmed-milk powder, 5 per cent linseed oil meal, 5 per cent bone meal and 1 per cent sodium chloride. In animals raised and maintained on this diet spontaneous peptic ulcer did not develop. A routine examination of 1,000 guinea-pigs which either died spontaneously or were killed during various experiments failed to reveal an instance of peptic ulcer.

Experiment 1.—(Feb. 17, 1928.) Eleven adult guinea-pigs were given a diet of autoclaved milk, rolled oats and hay ad libitum. This diet was almost completely deficient in vitamin C and relatively deficient in vitamins A and D. After three weeks the animals lost weight, and a few showed swollen gums, suggesting

12. Hess, A. F.: Scurvy, Past and Present, Philadelphia, J. B. Lippincott Company, 1920.

13. Magee, H. E.; Anderson, W., and McCallum, J.: Diet and Peptic Ulcer in Cavies, Lancet **1**:12 (Jan. 5) 1929.

14. Jackson, Leila, and Moore, J. J.: Studies in Experimental Scurvy in Guinea Pigs, J. Infect. Dis. **19**:478, 1916.

15. McCollum, E. V., and Pitz, W.: Vitamin Hypothesis and Deficiency, J. Biol. Chem. **30**:229, 1917.

16. Cohen, B., and Mendel, L. B.: Experimental Scurvy of the Guinea Pig in Relation to the Diet, J. Biol. Chem. **35**:425, 1918.

17. Sherman, LaMer and Campbell: Quantitative Determination of the Anti-scorbutic Vitamin C, J. Am. Chem. Soc. **44**:165 (Jan.) 1922.

scurvy. Each animal was then given a single administration of 5 cc. of canned tomato juice by pipet. The scorbutic symptoms disappeared but recurred within a week. This procedure was repeated a number of times in an effort to keep the animals in a prescorbutic state. All died between the sixth and eighth weeks of the experiment. At necropsy three of the guinea-pigs presented peptic ulcers. In one there were multiple ulcers on the lesser curvature of the stomach near the pylorus; in another both duodenal and pyloric ulcers were present (fig. 1), and in the third, a large perforated ulcer in the first portion of the duodenum, with a generalized peritonitis (fig. 2). A fourth animal showed an erosion of the mucosa of the duodenum. All animals presented varying degrees of scorbutic changes in the epiphyses, subcutaneous tissues, gums and suprarenals.

EXPERIMENT 2.—(Feb. 17, 1928.) Ten adult guinea-pigs were given the same diet as in experiment 1, and similarly maintained in a prescorbutic state by periodic

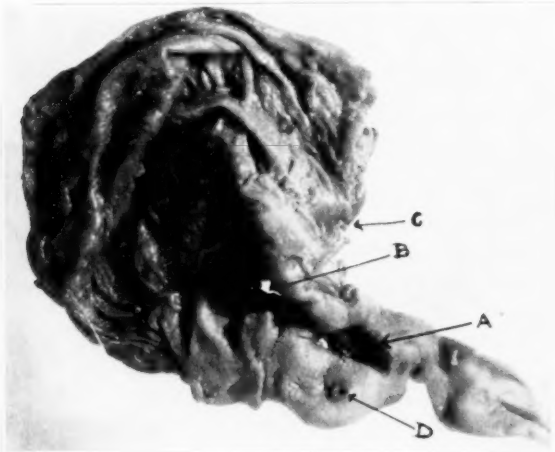

Fig. 1.—Perforated duodenal and pyloric ulcers. *A*, duodenal ulcer; *B*, pyloric ulcer; *C*, lesser curvature of the stomach, and *D*, ampulla of Vater.

administration of tomato juice. In addition they received 1 mg. of a culture of human tubercle bacilli in gelatin capsules by mouth twice each week. All animals died between the sixth and eighth weeks. At necropsy three animals presented peptic ulcers in the duodenum; one of these was an acute hemorrhagic lesion, whereas the others were deep and crater-like, with indurated walls. One ulcer perforated, producing a generalized peritonitis. All the animals presented scorbutic changes comparable to those noted in experiment 1. Two animals had small tuberculous ulcers in the cecum. The ulcers in the duodenum, however, were not tuberculous, as was demonstrated by microscopic sections.

EXPERIMENT 3.—(Feb. 17, 1928.) Ten adult guinea-pigs were given the same basic diet used in experiments 1 and 2, but supplemented by 8 cc. of tomato juice and 0.3 cc. of cod liver oil daily. The tomato juice was fed to each animal with a pipet, and the cod liver oil was given in capsules. One milligram of a culture of human tubercle bacilli was given in capsules twice each week. The animals remained in excellent condition for two months. Two died between the second and

third months of generalized tuberculosis. The remaining eight animals had extensive tuberculous lesions of the liver, spleen and lungs when they were killed after three and one-half months. One of the animals had a peptic ulcer on the lesser curvature of the stomach. None of the remaining nine animals showed any evidence of scurvy or of peptic ulcer at necropsy.

Comment on Experiments 1, 2 and 3.—In three of eleven adult guinea-pigs maintained on a diet partially deficient in vitamins A, C and D peptic ulcers developed. Most of the remaining eight animals showed congestion, hemorrhage or superficial erosions in the duodenum. Ten adult guinea-pigs were given the same diet and in addition fed tubercle bacilli. In three of the animals duodenal ulcers developed which were not tuberculous, as shown by microscopic sections. In experiment

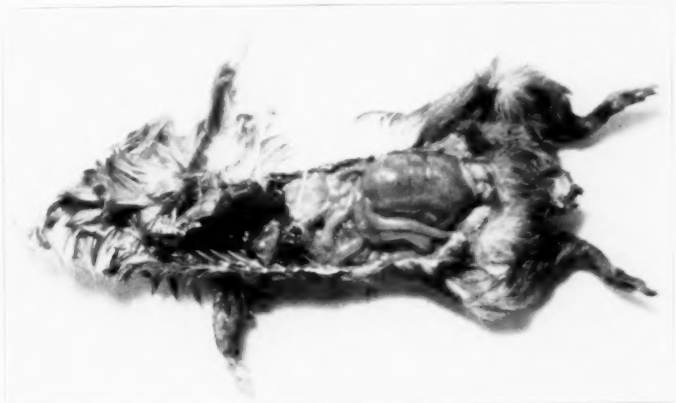

Fig. 2.—Arrow points to perforated ulcer of the first portion of the duodenum.

3, ten guinea-pigs were given the basic diet used in experiments 1 and 2, and tubercle bacilli by mouth, as in experiment 2, but the diet was supplemented by 0.3 cc. of cod liver oil and 8 cc. of tomato juice daily. Although in these animals extensive generalized tuberculosis developed, only one showed peptic ulcer. This indicates that the ulcers found in experiment 2 were due to the deficient diet and not to the action of the tubercle bacilli.

In experiments 1 and 2, as in those of Holst and Frölich[9] and McCarrison,[18] the diets were probably deficient in vitamins A and D, as well as in vitamin C. The diets of Magee and Anderson and McCallum[13] were deficient in minerals as well as in vitamin C. In the following studies we attempted to determine what deficiency of vitamin or vitamins is responsible for peptic ulcer.

18. McCarrison (footnotes 10 and 11).

EXPERIMENT 4.—(April 4, 1929.) We employed the scorbutic diet of Sherman, LaMer and Campbell,[17] which is deficient in vitamin C alone. Ten guinea-pigs were given this diet, which consists of whole ground oats, 59 per cent; skimmed milk powder (treated with heat to destroy the vitamin C), 30 per cent; butter fat, 10 per cent, and salt, 1 per cent. This diet is completely deficient in vitamin C. The animals lost weight rapidly after the second week. They were killed between the sixteenth and the twenty-second days of the experiment. Two showed acute ulceration limited to the mucosa of the duodenum. Seven presented hemorrhage into the ampulla of Vater. Only one guinea-pig had a normal intestinal tract. All ten animals presented the characteristic signs of scurvy in epiphyses, subcutaneous tissue, gums and suprarenal glands.

Ten control guinea-pigs were given the same diet supplemented by 8 cc. of tomato juice. All of them remained in good health and at necropsy six weeks later presented no abnormalities.

EXPERIMENT 5.—(Aug. 1, 1929.) As vitamin B is known to be related to certain intestinal disturbances, we performed the following experiment to determine whether a lack of this vitamin in the diet would produce intestinal ulcers.

Five guinea-pigs weighing from 250 to 300 Gm. were fed on water and the following mixture ad libitum: polished rice, 79 per cent; casein, 20 per cent, and salt, 1 per cent. This was supplemented by 0.3 cc. of cod liver oil daily to supply vitamins A and D and 10 Gm. of banana daily to supply vitamin C. The oil and the banana were fed to each animal individually. The banana is fairly rich in vitamin C and very poor in vitamin B. No hay was allowed, the animals being bedded on sawdust. After two weeks on this diet the guinea-pigs lost their appetites. At this time small amounts of brewer's yeast were given at irregular intervals in an effort to restore their appetites. All five animals died between the fourth and sixth weeks of the experiment. Peripheral neuritis developed in two of them. Two had severe diarrhea, and one died with a volvulus of the ileum. General atrophy of the intestinal mucosa was found but no evidence of scurvy in the gums, epiphyses, subcutaneous tissue or suprarenal glands, and no hemorrhage or ulceration in the stomach or duodenum.

Comment on Experiments 4 and 5.—Experiment 4 indicates that peptic ulcer in the guinea-pig is a result of deficiency in vitamin C alone. The addition of vitamins A and D to the diet failed to prevent the appearance of the ulcers, while the presence of vitamin C completely prevented their development. In experiment 5 the diet deficient in vitamin B produced lesions characteristic of deficiency in vitamin B, but there were no hemorrhages in the intestinal mucosa and no evidence of peptic ulceration.

It is conceded that under ordinary conditions man practically never lives on a diet as completely deficient in vitamin C as that used in experiment 4. We thought it advisable to see how closely we could imitate the diet eaten by the ordinary human being and still obtain the development of chronic peptic ulcers in guinea-pigs. We found that we could give most of the staple articles of the human diet, provided fresh fruits and fresh vegetables were omitted. A mixture was made which contained 20 per cent of baker's white bread (dried and ground) 20 per cent of chipped beef (ground and dried), 20 per cent of potato chips

(ground), 15 per cent of uncooked rolled oats, 15 per cent of skimmed milk powder and 10 per cent of sugar. Salt was present in the potato chips and chipped beef. This mixture is quite palatable even to the human taste, and the guinea-pigs ate it with relish. The skimmed milk powder was not heated to destroy its content of vitamin C; so the diet was only partly deficient in this vitamin. For the sake of convenience, we shall refer to this as human diet 2. That this diet is not inherently injurious to guinea-pigs is shown by an experiment in which we raised young guinea-pigs to maturity on it by adding cod liver oil, 0.3 cc., and tomato juice, 8 cc., daily. The guinea-pigs failed to deliver living young. When a few cabbage leaves were supplied, however, breeding took place in a normal manner.

EXPERIMENT 6.—(March 3, 1929.) Ten adult guinea-pigs were given human diet 2, hay and water ad libitum. They ate with avidity and grew very fat. Between the third and fourth weeks of the experiment the appetite began to fail, and the animals died between the eighth and twelfth weeks. Two of the ten animals had duodenal ulcers, one of which perforated. At necropsy there was very little evidence of scurvy, but most of the animals showed either congestion, hemorrhage or superficial erosion of the duodenum.

EXPERIMENT 7.—(May 25, 1929.) Eight adult guinea-pigs were given human diet 2 with hay and water ad libitum, supplemented by 0.3 cc. of cod liver oil daily. The cod liver oil was fed individually to the guinea-pigs from a syringe. Two died of perforated duodenal ulcers, one at the end of the second month and another at the end of the fourth month. The latter ulcer had the macroscopic and microscopic characteristics of a chronic peptic ulcer. All animals were well nourished and presented only slight evidence of scurvy other than congestion and hemorrhage into the duodenum.

EXPERIMENT 8.—(May 25, 1929.) Ten adult guinea-pigs were given human diet 2, hay and water ad libitum. In five animals this diet was supplemented by 10 cc. of tomato juice, and in the other five, by 10 cc. of tomato juice and 0.3 cc. of cod liver oil. All the animals remained in excellent nutrition until they were killed four months later, when no evidence was found of scurvy or of ulceration in the intestinal tract.

Comment on Experiments 6, 7 and 8.—With this diet of bread, meat, milk, potatoes, rolled oats and sugar, peptic ulcers developed in four of eighteen guinea-pigs. The addition of cod liver oil to the diet did not prevent the development of the ulcers, whereas the daily addition of 10 cc. of tomato juice completely protected the animals from the lesions.

In experiments 9 and 10 the relation of diet to intestinal tuberculosis and peptic ulcer was again investigated.

EXPERIMENT 9.—(April 15, 1929.) Twenty-one adult guinea-pigs were given water, hay and human diet 2 ad libitum. In addition, 0.5 cc. of sputum which contained tubercle bacilli was given daily with a 1 cc. tuberculin syringe. The animals received periodically small doses of tomato juice, as in experiments 1 and 2. They died from one to three months later, and several had tuberculous

ulcers of the ileum. In addition, three duodenal ulcers and one jejunal ulcer were found, the latter having perforated. Microscopic study revealed no evidence of tuberculosis in the peptic ulcers. Most of the animals showed mild lesions of scurvy, but some did not. Several of the animals showed congestion, hemorrhage and erosion of the duodenum.

EXPERIMENT 10.—(April 15, 1929.) Thirty-six adult guinea-pigs were given water, hay and human diet 2 ad libitum. They all received daily 0.5 cc. of sputum which contained tubercle bacilli. In ten animals the diet was supplemented by 10 cc. of canned tomato juice daily; in sixteen, by 0.3 cc. of cod liver oil and 10 cc. of canned tomato juice, and ten received daily two or three cabbage leaves each, as a supplementary feeding. A few animals died between the second and third months of the experiment with generalized tuberculosis. The others were killed at the end of the fourth month, when the experiment terminated. None of the thirty-six animals presented any evidence at necropsy of hemorrhage or ulceration of the intestinal tract.

Comment on Experiments 9 and 10.—Of the twenty-one guinea-pigs maintained on human diet 2 and fed with sputum containing tubercle bacilli, duodenal ulcers developed in three, and a jejunal ulcer in one. That tubercle bacilli were not a factor in causing these ulcers is shown by experiment 10, in which thirty-six guinea-pigs were fed tuberculous sputum and maintained on the same diet supplemented by either tomato juice, cod liver oil and tomato juice, or cabbage leaves. None of the thirty-six animals fed on this supplemented diet presented lesions in the stomach or duodenum, although they all had extensive generalized tuberculosis.

The initial break in the mucosa in peptic ulcer may be caused by a variety of agents: mechanical, chemical, nervous, bacterial or dietary. But if our theory is correct, an abundance of vitamin C is essential for healing, regardless of the primary cause. In the following experiment mechanical injury was done to the mucosa of the stomach and duodenum. Some animals were maintained on an adequate diet throughout the experiment, and others were given an adequate diet only after operation, while still others were on an inadequate diet throughout. Comparative studies were made on the healing of ulcers in the animals of different groups.

EXPERIMENT 11.—(April 15, 1929.) Fifteen normal adult guinea-pigs were selected. Five of them were fed on our ordinary stock diet throughout the experiment, and served as control animals. The other ten animals received a diet of rolled oats, autoclaved milk and hay ad libitum, supplemented by 0.3 cc. of cod liver oil fed individually each day. After fifteen days of this diet none of the animals showed gross evidence of scurvy, although we knew from previous experiments that scurvy would have appeared in an additional week or ten days.

All animals were subjected to the following procedure: They fasted for twenty-four hours previous to the operation. Each one was given 5 cc. of a 50 per cent solution of dextrose immediately before the operation. Under ether anesthesia the peritoneum was opened, and a purse-string suture with silk was made in the ante-

rior wall of the stomach. Through the center of this an opening was made with a cautery. A dental burr was then introduced as far as the duodenum, and the mucosa of the duodenum was scarified. The dental burr was withdrawn, and the opening in the stomach was closed with the purse suture. The peritoneum, the muscle, the subcutaneous tissue and the skin were in turn sutured with black silk. Each of the animals was given 5 cc. of a 50 per cent solution of dextrose immediately after the operation. One of the fifteen guinea-pigs died at the induction of the anesthesia. This animal, which had been fed the deficient diet for fifteen days, was found to have an erosion in the mucosa of the duodenum, although there was

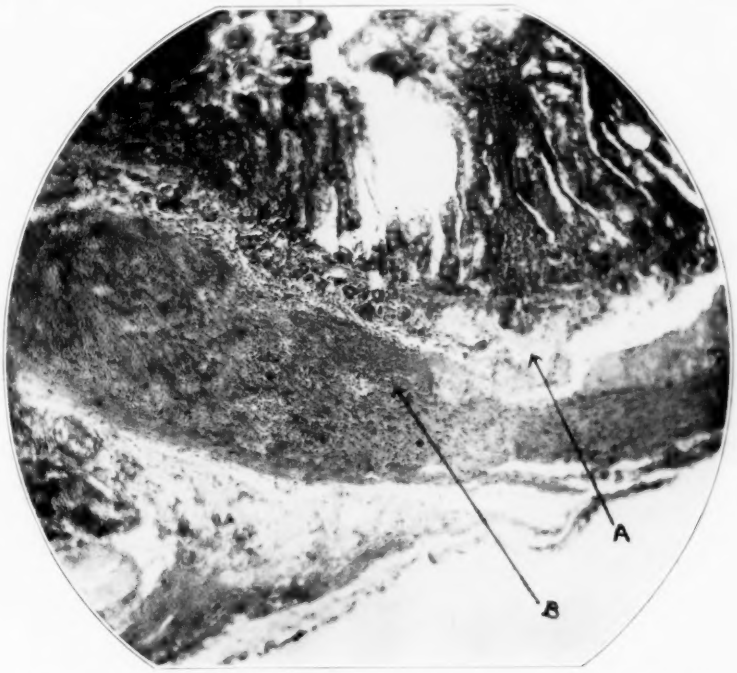

Fig. 3.—Hemorrhage into the wall of the duodenum with necrosis and sloughing of part of the mucosa. *A*, hemorrhage into the submucosa; *B*, hemorrhage into the muscularis.

no gross evidence of scurvy in other parts of the body. The remaining animals survived; in none of them did peritonitis develop.

Five guinea-pigs were maintained on the stock diet throughout the experiment. Five of the ten animals which were fed on the diet deficient in vitamin C before operation remained on that diet. The other four animals on this diet previous to operation were subsequently given 10 cc. each of canned tomato juice daily. Although there was no evidence of scurvy in these nine guinea-pigs at the time of operation, it was noted that they bled more readily, and that the edges of the cut tissues became more hemorrhagic and edematous following operation than did the wounds in the animals on an adequate diet.

The incision in the skin of the five animals fed on the stock diet was completely healed in ten days, and when the animals were killed three weeks later, the mucosa of the duodenum was so well restored that it was impossible to see any evidence of previous injury. The cautery wound into the wall of the stomach was entirely healed, and was located only by the presence of the black silk suture.

In the four animals which were fed a diet deficient in vitamin C before the operation and which were given tomato juice afterward the incision in the skin also healed completely after eighteen days. When the animals were killed three weeks after the operation, the mucosa of the stomach and the duodenum was likewise restored to normal. There was still, however, some edema of the subcutaneous tissue.

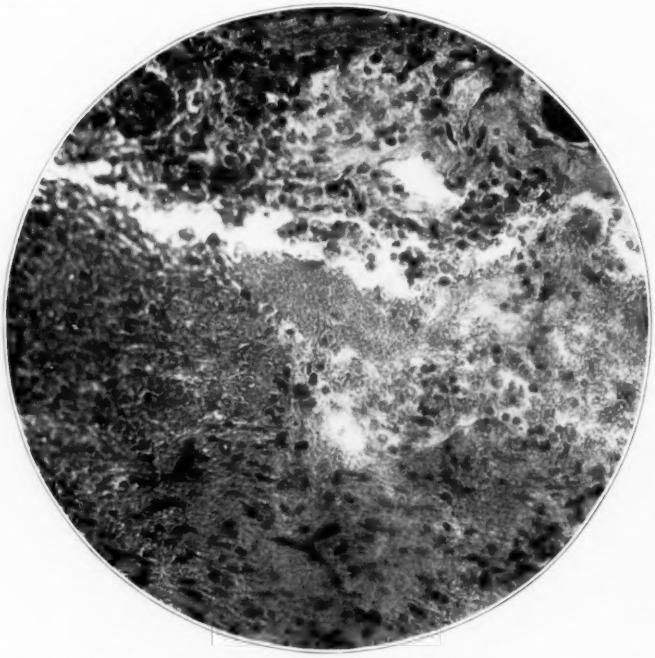

Fig. 4.—A higher magnification of the hemorrhagic areas in the submucosa and muscularis seen in figure 3. The area in the center of the photograph consists mainly of disintegrated red cells. There is an occasional intact red blood cell.

The five guinea-pigs which remained on the diet deficient in vitamin C throughout the experiment died from one to two weeks after the operation. The incision in the skin showed no evidence of healing; the cautery wound of the stomach showed ulcers in two animals, and four of the five showed large ulcers in the duodenum.

Comment on Experiment 11.—Fourteen adult guinea-pigs were subjected to operative trauma of the stomach and duodenum. Five animals used as controls were maintained on an adequate diet throughout the

experiment, and were killed three weeks after the operation. At necropsy no lesions were observed in the intestinal tract, and the wounds in the stomach and duodenum were found to be soundly healed.

The nine animals fed on a diet deficient in vitamin C were operated on on the fifteenth day of the experiment, while they were still in the prescorbutic stage. It was observed that they bled more freely, and that more edema of the injured tissues developed in them than in the controls.

Five were kept on the scorbutic diet after the operation. The operation consisted of mechanical removal of the mucosa from a portion of the duodenum. All the animals died between the seventh and fourteenth days following operation. Two presented ulcers at the site of the operative wound in the stomach, and four of the five animals showed large

Fig. 5.—Low power magnification of a section taken from a duodenal ulcer which showed chronic changes in the floor.

duodenal ulcers. The four animals which were fed on a diet deficient in vitamin C before operation but which were given tomato juice subsequently recovered completely; no ulcers were present. The operative wound in the abdominal wall, however, was slower in healing in these animals than in those given an adequate diet throughout the experiment.

These experiments indicate that in the absence of an adequate supply of vitamin C, mechanical injury to the mucosa of the stomach and duodenum of the guinea-pig results in the development of ulcers. The same degree of mechanical injury in animals fed on a diet adequate in vitamin C results in rapid and complete healing.

PATHOLOGY

The usual site of the ulcers in the foregoing experiments was in the first portion of the duodenum just distal to the pyloric sphincter. A

few were present in the stomach in the pyloric portion near the lesser curvature. Single ulcers were the rule, and they were usually round or oval. Although a few ulcers presented irregular borders, most of them were punched-out in appearance. There was usually sufficient induration of the walls of the ulcer to be easily palpated from the outside of the viscus. Both perforation of the ulcers and fatal hemorrhage occurred several times. Lesser hemorrhages from the ulcer occurred more frequently, and extravasation of blood into the wall of the bowel was the most constant finding.

Figure 3 represents a section taken from a hemorrhagic area in the wall of the duodenum. Hemorrhage is present in the submucosa and

TABLE 1.—*Results of Experiments with Chronic Deficiency in Vitamin C*

Experiment	Number of Animals	Number of Peptic Ulcers
1	11	3
2	10	3
4	10	2
6	10	2
7	8	2
9	21	4
11	5	4
	75	20

TABLE 2.—*Results of Experiments with Adequate Vitamin C*

Experiment	Number of Animals	Number of Peptic Ulcers
3	10	1
4 (control)	10	0
5	5	0
8	10	0
10	36	0
11 (control)	9	0
	80	1

muscularis. The mucosa overlying the hemorrhage is necrotic, and part of it has sloughed out. A higher magnification of the submucosa and muscularis (fig. 4) shows a few intact red blood cells in the midst of many disintegrated cells.

Although most of the ulcers observed in our experiments were acute, some of them presented evidence of a chronic nature. Figure 5 is the study of a duodenal ulcer that occurred in an animal which had been fed the diet deficient in vitamin C for four months. A higher magnification of this lesion (fig. 6) shows round cell infiltration and a considerable number of fibroblasts in the floor of the ulcer.

Whether or not there is an initial thrombosis of the vessels in the area of the ulcer we are at present unable to say. In any case, hemorrhage into the wall of the duodenum in the region overlying the ulcer was an almost constant finding.

TREATMENT OF PEPTIC ULCER IN MAN

The experiments recorded here indicate that peptic ulcer in the guinea-pig is due to a partial but chronic deficiency of vitamin C. This specific deficiency may or may not be the cause of peptic ulcer in man. If it is the cause, an abundance of vitamin C in the diet should aid in the healing of these lesions.

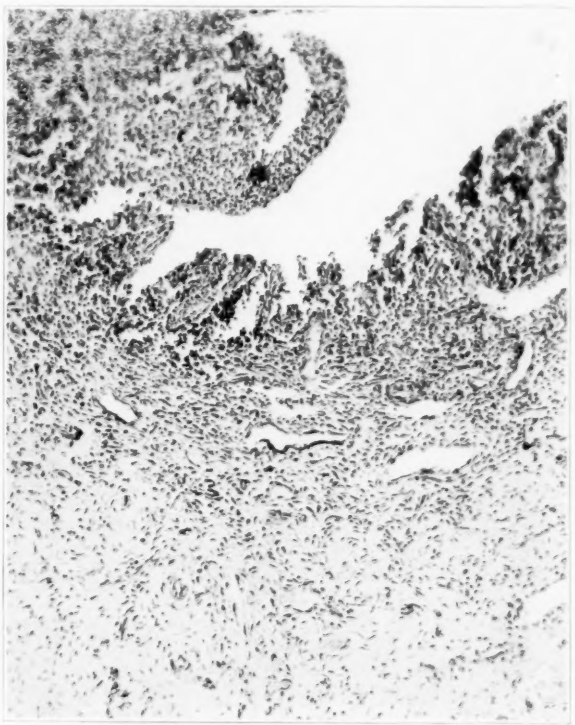

Fig. 6.—Higher magnification of the section in figure 5. Note the round cell infiltration and numerous fibroblasts in the floor of the ulcer.

Five patients with chronic duodenal ulcers have been treated at the sanatorium by supplementing the ordinary hospital diet with cod liver oil and tomato juice. This is the routine dietary for the treatment of intestinal tuberculosis at the New York State Hospital for Incipient Pulmonary Tuberculosis [18] and contains an abundance of other vitamins which may possibly be of value in the treatment of peptic ulcer. The number of patients treated is too small to warrant definite conclusions, but the small group responded favorably to the treatment for periods

ranging from six months to three years. Therefore it might be advisable to supplement the Sippy or Lenhartz diet with tomato or orange juice and cod liver oil.

CONCLUSIONS

1. Routine necropsies on 1,000 guinea-pigs maintained on our stock diet failed to show a single spontaneous peptic ulcer.

2. Of seventy-five guinea-pigs fed on diets deficient in vitamin C, in twenty, or approximately 26 per cent, peptic ulcers developed which were similar in location and in gross and microscopic appearances to those observed in man.

3. Of eighty guinea-pigs fed on corresponding basic diets supplemented by vitamin C, in only one did peptic ulcer develop.

4. Diets deficient in vitamins A, B and D did not cause peptic ulcers if the supply of vitamin C was adequate.

5. Mechanical injury to the mucosa of the duodenum in guinea-pigs fed on an adequate diet was followed by rapid and complete healing, while similar injury to guinea-pigs fed on a diet deficient in vitamin C resulted in the formation of peptic ulcers.

6. Peptic ulcer in the guinea-pig is apparently caused by a partial but prolonged deficiency of vitamin C.

INHERENT SENSITIVITY OF THE SKIN TO NICKEL AND COBALT

(ALLIED ELEMENTS IN GROUP VIII, PERIODIC SYSTEM)

SLOAN G. STEWART, M.D.

PHILADELPHIA

Inherent sensitivity of the skin to nickel, in contrast to the acquired form, which has been found so frequently among those who work with nickel, seldom has been described. Allusions are made, however, to a "natural" susceptibility among certain workers, especially blond people and young women. Indeed, a real distinction may be made between inherent and acquired sensitivity of the skin to external sensitizing agents. In that group in which sensitiveness to nickel is acquired are placed those cases of "irritative dermatitis" in which, by repeated contact of the skin with solutions of nickel salts or finely divided particles of nickel dust, an eruption develops at the site of exposure. This does not imply a latent sensitivity, for after a certain period of exposure this lesion may develop under certain conditions of heat and moisture in any person exposed for a sufficiently long period. Quite analogous is the experiment described by Walthard,[1] in which he was able to produce a nickel dermatitis in guinea-pigs by repeatedly painting the skin with nickel sulphate.

The dermatitis of acquired sensitivity to nickel, usually occurring on the face, neck and other exposed parts, constitutes an important problem in industrial hygiene. The first comprehensive review of metal dermatitis, alluding to nickel dermatitis in workers exposed to nickel baths in the plating process, is that of Blaschko,[2] in 1889. This has been followed by extensive industrial surveys concerning the cause and prevention of nickel dermatitis, the most comprehensive of which are treatises by White,[3] Blumer and Mackenzie,[4] and Gron.[5]

From the Allergy Section of the Medical Clinic, Hospital of the University of Pennsylvania.

1. Walthard, B.: Die Erzeugung experimenteller Nickelidiosynkrasie bei Laboratoriumstieren, Schweiz. med. Wchnschr. **56**:603, 1926.

2. Blaschko, A.: Die Berufsdermatosen der Arbeiter, Deutsche med. Wchnschr. **15**:925, 1889.

3. White, R. P.: The Dermatergoses or Occupational Affections of the Skin, ed. 3, London, H. K. Lewis & Co., 1928.

4. Blumer, F. M. R., and Mackenzie, E. A.: Studies in the Control and Treatment of "Nickel Rash," J. Indust. Hyg. **8**:517, 1926.

5. Gron, K.: Nickelplater's Rash, Urol. & Cutan. Rev. **33**:606, 1929.

In the group of cases designated as showing inherent sensitivity to nickel are included those in which there is found a generalized sensitivity of the skin of the body to nickel when there has been no exposure to the metal. Inherent sensitivity may be similar to the so-called "focal sensitivity" of the skin, caused by absorption of a substance through the skin at one point producing sensitization of other parts through the blood stream. The extreme rarity of the condition, however, makes this explanation seem unlikely, when one considers how often nickel-containing objects touch the skin. Examples of inherent sensitivity to nickel are not common in the medical literature, and the brevity of most of the reports and the types of cases presented do not give an adequate clinical picture. In two of three reports that will be noted, the cutaneous lesions might be thought to be an irritative dermatitis, were it not for suggestive but inadequate patch tests.

McAlester, Jr., and McAlester, III,[6] reported three cases of nickel dermatitis, with lesions involving the nose and the eyelids; the inception was in nickel used in white gold frames of spectacles. Patch tests to nickel made with a nickel coin on the forearm were positive. Three similar cases of dermatitis over the temples and ears were described by Lain.[7] This rash was relieved by the use of frames of glasses free from nickel. No cutaneous tests were made. In Rothman's[8] case is recounted the history of a counter of coins who worked for a tramway company and in whom "eczema" developed. Skin tests with nickel, silver and copper coins revealed a strongly positive reaction to nickel and a slightly positive reaction to silver and copper. Pure metals, however, were not used in the testing.

Inherent sensitivity of the skin to closely allied metals in the same (periodic) group, as observed for nickel and cobalt in the patient whose case is reported in this paper, must be most uncommon, for no description of this phenomenon has been found in the medical literature. This may be due to the fact that patch tests with pure metals have not attained the peak of prominence in dermatology and allergy that skin tests to pollens, foods and animal emanations have acquired, with the possible exception of the use of patch tests in determining sensitivity to arsphenamine.

REPORT OF A CASE

History.—A. G., a woman, aged 31, was seen as a private patient for desensitization to hay fever which occurred in the fall. The characteristic symptoms of hay fever had persisted for twelve years, starting about August 15, and lasting until the

6. McAlester, A. W., Jr., and McAlester, A. W., 3d: Nickel Sensitization from White Gold Spectacle Frames, Am. J. Ophth. **14**:925, 1931.

7. Lain, E. S.: Nickel Dermatitis, J. A. M. A. **96**:771 (March 7) 1931.

8. Rothman, S.: Hypersensitiveness to Metal Coins, J. A. M. A. **97**:336 (Aug. 1) 1931.

first cold weather. Occasionally sneezing and epiphora were noted in the spring. Mild paroxysms of asthma occurred twice during the fall of 1931. Previous inoculations of pollen had been unsuccessful in effecting desensitization. Three years before, frequent outbreaks of "hives" had been the source of much discomfort, but had not been present during the past year. There had been no eczema. Two or three times a year, for several years, the patient had had attacks of nausea and vomiting, associated with mild left frontal headache. There was also a history of the development of itching papules and vesicles on the skin at various points of friction after exertion in hot weather. This was most marked in the antecubital spaces and the axillae.

The most unusual feature of this exceptionally allergic history related to an itching, burning rash described as "welts on the skin, which sometimes caused blisters and redness." The lesions always appeared at the sites of contact with certain metal objects in wearing apparel, such as a particular white gold wrist

TABLE 1.—*Cutaneous Sensitization Tests (Scratch Tests)*

a. Inhalants:			
Chicken feather	0-5	Kapok	5-10
Goose feather	3-15	Cottonseed	5-20
Horse hair	4-12	Orris root	5-35
Sheep wool	2-5	Silk	4-8
Stock dust	6-25		
b. Foods:			
Egg	0	Orange	3-10
Wheat	0	Lettuce	5-20
Milk	0	Vanilla	3-15
Coffee	3-15	Tea	0
c. Pollens:			
Ragweed, giant	12-30	June grass	3-15
Ragweed, short	15-35	Orchard grass	4-15
Goldenrod	10-20	Timothy	5-15
Sweet vernal	3-10		

0 indicates a negative reaction; in readings recorded by two figures (3-15), the first figure (3) represents the diameter of the wheal in millimeters, and the second (-15), the diameter of the areola in millimeters.

watch, a gold bracelet, safety pins, suspensories and the like. The eruption would persist for from two to ten days. Yellow gold, silver and platinum induced no reaction.

The past medical history was unimportant except for the presence of a colloid goiter since puberty, which at times, especially during the past three years, increased somewhat in size.

The only family history of allergy was in the father, who for years had had hay fever. There was no history of urticaria, cutaneous disease or asthma.

Physical Examination.—The patient was an active, healthy, cooperative person. The only positive findings on examination were hyperactive reflexes, a definite vasomotor instability and a diffuse, symmetrical enlargement of the thyroid gland. The blood pressure was 115 systolic and 80 diastolic, with an average pulse rate of 80.

Laboratory Data.—The urine was normal. The red blood count averaged 4,600,000 cells, with a hemoglobin content of 82 per cent (Sahli). The leukocyte count was 9,000, with a normal differential count. At no time was eosinophilia found. The Wassermann reaction of the blood was negative. The basal metabolic

rate varied from —5 per cent to +1 per cent. In table 1 are summarized the cutaneous tests to pollens, inhalants and foods:

Sensitization Tests of the Skin.—There was cutaneous sensitivity to all of the pollens tested, to many of the inhalants and to a few foods, but of these, symptoms were produced only by giant and short ragweed. Desensitization with these pollens gave great relief from symptoms due to ragweed during each of the past two seasons.

The clinical impression of multiple allergic reactions in the form of hay fever and asthma due to ragweed, urticaria, heat sensitivity and possibly migraine of mild type did not explain the peculiar cutaneous reaction experienced by contact with the accessory metallic articles used in feminine wearing apparel.

Patch Tests for Sensitivity to Metals.—In accordance with the technic instituted by Jadassohn [9] and reviewed by Schoch [10] in working with arsphenamine, patch tests of the skin were made, only pure elements of metals being used, especially those necessary for compounding in alloys. It seemed likely from the history that the specific irritating substance would be found among the latter metals, because all of the offending articles were made of alloyed metals, whereas articles of yellow gold, silver and platinum produced no eruption. A strong sensitiveness to nickel was discovered, as recorded in table 2.

TABLE 2.—*Cutaneous Sensitization Tests (Patch Tests)*

a. Metals:			
Zinc	0	Gold	0
Tin	0	Nickel	++++
Lead	0	Cobalt	+++
Aluminum	0	Iron (1)	+
Copper	0	Iron (2)	0
Silver	0		

The positive reaction obtained in specimen 1 of iron was a false positive reaction due to 1 per cent of contamination by nickel. Specimen 2 of iron contained no nickel.

The sensitivity of the skin to cobalt was determined only after the patient had brought a string of bluish-green beads that had caused an urticaria-like eruption encircling the neck. The coloring pigment was the silicate of cobalt. By patch test, as seen in the chart, cobalt gave almost as strong a cutaneous reaction as nickel. Since cobalt and nickel are in the same periodic metal group with iron, in the ferrous series, patch tests were made with a small square of what was thought to be pure iron, but was subsequently found to contain traces of nickel, with a resultant slightly, but definitely, positive cutaneous reaction. Other metals chosen from the first four groups of the periodic table gave negative patch tests. Control patch tests made on fifteen normal and allergic persons were negative.

Type of Cutaneous Lesion.—The lesion represented in figure 1 was produced after twenty hours' contact with metallic nickel. It was deep purple, slightly indurated with local edema, and covered with coalescing papular and vesicular efflorescences, which in small areas formed weeping surfaces. This lesion produced intense itching and a sensation of burning. Some of the smaller areas of dermatitis lasted only a few days, but the large areas produced by strongly positive tests

9. Jadassohn, J.: Hautkrankheiten bei Stoffwechselanomalien, Fifth Internat. Dermat. Cong. 1904, vol. 2, p. 231.

10. Schoch, A. G.: Arsphenamine Sensitization Tests Including a Report of Arsenical Dermatitis Due to Arsenobenzol Radical of Bismarsen, Am. J. Syph. **14**:75, 1930.

Fig. 1.—Photograph of patch tests with (1) aluminum, (2) copper and (3) nickel applied to the inner thigh. Note the swelling and the small vesicles where the nickel was in contact with the skin. Tests 1 and 2 were negative.

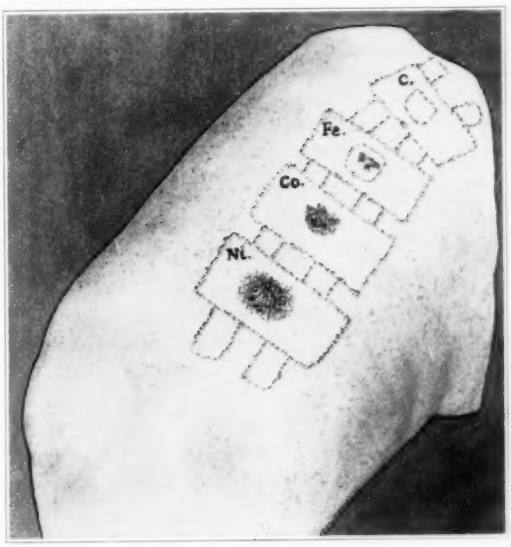

Fig. 2.—This sketch represents graphically the hyperemic, edematous, vesicular lesions produced by contact of nickel, *Ni*, cobalt, *Co*, iron, *Fe*, and a control metal, *C*, of equal size, with the skin of the patient.

persisted for as long as two or three weeks. This type of lesion has been classified as dermatitis venenata—a nonspecific term including such reactions as those produced by Rhus toxicodendron, Primula obconica, other plants and shrubs, arsphenamine and drug and chemical irritants.

Patch Tests and Passive Transfer.—The patch tests were strongly positive to nickel and cobalt on any surface of the patient's skin, and, since there had never been any more exposure to nickel than occurs in the average nonsensitive person, it did not seem possible that the condition could be an acquired sensitiveness. No one in the patient's family had been in contact with nickel or cobalt, and patch tests with the same group of metals as were used on the patient were negative when applied to the father's and mother's skin. Passive transfer tests were done on a normal, nonallergic person according to the Prausnitz-Küstner method. Patch tests with nickel, cobalt and iron on the passive transfer areas were negative, and with ragweed pollen by scratch test, strongly positive. Patch tests with all of the metals on normal areas of skin were negative. There is no evidence that a specific substance circulates in the blood to cause this altered capacity for specific reaction in the skin to metallic antigens. This is in agreement with the negative results obtained by Lewith [11] and by Walthard [1] with nickel salts, and by Kesten and Laszlo [12] with other antigens causing dermatitis venenata.

Nature of the Cutaneous Reaction.—The dermatitis resulting from contact with nickel was identical with that produced by cobalt. The speed of reaction when the pure metals were used varied from eight to sixteen hours, being influenced greatly by temperature and humidity, and secondarily, as will be pointed out in relation to the salts, by the solubility and rate of dissociation of those salts which form with perspiration. On cold days only a slight reaction could be induced in twenty-four hours by patch test. On hot days, and especially when the humidity was high, not only did the lesions appear more quickly, but they were much more intense. Reduction of the skin's resistance and increased irritability result from excessive alkaline sweat under such conditions (Pemberton [13]) and probably explain, in part, the variability of this reaction.

Lewith [11] in his investigations on those who worked with nickel made intradermal tests with various nickel salts and obtained positive reactions only with nickel sulphate. Control tests with 1 per cent sulphuric acid and with zinc and copper sulphate gave negative results. Schittenhelm and Stockinger,[14] using intracutaneous injections and compresses of nickel sulphate and chloride, obtained strongly positive reactions on previously attacked parts of the skin ("focal reaction").

In table 2 are summarized the results obtained from patch tests in which the crystals of various salts of nickel, cobalt and iron were used, applied to the skin of the patient, A. G., in dry form and sealed under gauze with squares of adhesive tape.

---

11. Lewith: Verhandl. Dermat. Gesellsch. d. Tschechoslowakô Republic, Feb. 18, 1927; quoted by Gron.[5]

12. Kesten, B., and Laszlo, E.: Dermatitis Due to Sensitization to Contact Substances; Dermatitis Venenata, Occupational Dermatitis, Arch. Dermat. & Syph. **23**:221 (Feb.) 1931.

13. Pemberton, R.: A Summary of the Effects of External Heat Upon the Human Body, Am. J. M. Sc. **169**:485, 1925.

14. Schittenhelm, A., and Stockinger, W.: Ueber die Idiosynkrasie gegen Nickel und ihre Beziehung zur Anaphylaxie, Ztschr. f. d. ges. exper. Med. **45**:58, 1925.

Tests with Metal Salts.—The reactions listed in table 3 show definitely positive reactions to nickel and cobalt salts, as indicated by the plus marks. No rash was noted after application of either the unstable divalent or more stable trivalent salts of iron. This suggested the possibility of a false positive reaction to metallic iron. A chemical analysis of the metallic iron used for testing the skin revealed a contamination by nickel of less than 1 per cent. The patch test with iron was repeated, pure iron wire of high grade being used. After a negative cutaneous test with this was obtained, it was concluded that there was no skin sensitivity to iron. This experiment does serve, however, to illustrate the extreme delicacy of the reaction.

There was a variability in the intensity of the reactions, although the tests were performed under the same conditions of temperature and moisture. Another factor relating to the variability of these reactions must be the solubility and ionization of the salts of nickel and cobalt. The most violent reactions were produced by the nitrates. The solubility of the nitrates, sulphates and chlorides is recorded in table 3. The chlorides and acetates are also more soluble than the sulphates. A similar ratio applies at body temperature.

TABLE 3.—*Cutaneous Reactions to Salts of Nickel, Cobalt and Iron (Patch Tests)*

No.	Salts of Metals	Solubility at 30 C. Gm. Ni or Co 100 Gm. H_2O	Itching	Hyperemia	Edema	Vesicles
1	$NiCl_2$	29	+++	++	−	++
2	$Ni(NO_3)_2$	35	+++	++	+++	+++
3	$Ni(C_2O_2H_3)_2$	..	+++	+++	−−	−
4	$NiSO_4$	16	++	0	0	−
5	$CoCl_2$	26	+++	++	−−	+++
6	$Co(NO_3)_2$	36	++	+++	−	−
7	$Co(C_2O_2H_3)_2$	..	−	+	+−−	0
8	$CoSO_4$	16	+−	−	0	+
9	$FeSO_4$	..	0	0	0	0
10	$FeSO_4.(NH_4)_2SO_4$	..	0	0	0	0
11	$FeCl_3$	..	0	0	0	0
12	$(Fe)_2(SO_4)_3$	..	0	0	0	0

SUMMARY AND CONCLUSIONS

The patient whose case is presented exhibited an inherent skin sensitivity to nickel and cobalt. In summarizing the data obtained from metal patch tests, certain facts stand out definitely: There is a group-specific reaction of the skin to nickel and cobalt. This reaction takes the form of dermatitis venenata, a type of lesion which is not specific. The most important factors influencing the speed and extent of the reaction are heat, moisture and the solubility of the salts used. Lastly, the chemical nature of the reaction is further suggested in the patch tests by the decreased time it required to obtain a reaction to the metallic salts in comparison with the time required for a reaction to pure metals.

That the reaction is not irritative is proved by negative control tests. That it is not an acquired sensitivity is supported by a negative history of exposure to or ingestion of the specific metals. Passive transfer tests suggest that there is no specific reacting substance in the blood, and that the reaction is a direct cellular one.

It would seem likely, therefore, that there exists a reaction, chemical in nature, between some specific complex molecule in the epidermal cells and the salts of nickel and cobalt. It is questionable that this should be interpreted as a truly allergic phenomenon, but such a conclusion is strongly suggested because of the similarity of the condition to allergic types of dermatitis venenata and because of its association with a multiplicity of coexisting allergic manifestations exhibited by the patient, i. e., hay fever, asthma, urticaria and migraine.

DIRECT COMPARISON BETWEEN SPECIFIC AND NONSPECIFIC SERUM THERAPY FOR TYPE I LOBAR PNEUMONIA

WHEELAN D. SUTLIFF, M.D.

MAXWELL FINLAND, M.D.

AND

THOMAS N. HUNNICUTT, M.D.

BOSTON

It has been suggested that the effects of specific serum therapy in type I lobar pneumonia are due, not to the specific antibodies contained in the serum, but to the nonspecific action of the intravenously administered horse serum proteins. Miller [1] and von den Velden,[2] as well as Hallermann and Kähler,[3] have made this suggestion because of the symptomatic changes they noted in lobar pneumonia following the injection of protein materials other than immune horse serum, such as typhoid vaccine, normal horse serum and normal human serum. Sonnenfeld [4] and Lichtenstein [5] have supported this suggestion because they occasionally observed striking clinical improvement in patients with pneumonia due to pneumococci other than type I following the administration of serum that presumably contained only type I pneumococcic antibodies.

An examination of the question from the point of view of those who have had extended experience with the specific serum, however, brings out the fact that the symptomatic and curative effects of the serum are probably due to its content of type-specific pneumococcic

From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital, and the Department of Medicine, Harvard Medical School.

This study was aided, in part, by the William W. Wellington Fund of the Harvard Medical School.

1. Miller, J. L.: The Present Status of Nonspecific Therapy, J. A. M. A. **95**:464 (Aug. 16) 1930.

2. von den Velden, R.: Klinisch-experimentelle Beiträge zur Kenntnis temperatur-herabsetzender Substanzen, Deutsches Arch. f. klin. Med. **113**:324, 1913-1914.

3. Hallermann, A., and Kähler, H.: Ueber die Typeneinteilung der Pneumonie und ihre Behandlung mit Serum, Klin. Wchnschr. **9**:650, 1930.

4. Sonnenfeld, A.: Serumtherapie der kruppösen Pneumonie, Deutsche med. Wchnschr. **56**:569, 1930.

5. Lichtenstein, Hermann: Die Serumbehandlung der croupösen Pneumonie, Med. Klin. **25**:1966, 1929.

antibodies. In experimental animals the beneficial action of the antipneumococcic serum has repeatedly been shown to depend on its type-specific character,[6] and extensive, carefully compiled clinical data of its use in man point to the same conclusion.[7] But even though the therapeutic effect of antipneumococcic serum depends on its content of specific antibodies, it is probable that some nonspecific action is also present. The following observations were made in order to attack the question of the extent and nature of the nonspecific effects.

A comparison was made between the effects of concentrated type I antipneumococcic serum and the effects of similarly concentrated normal and antimeningococcic horse serums containing no specific pneumococcic antibodies. The regularity of the symptomatic changes following the administration of type I antipneumococcic serum [8] made it seem likely that such a comparison would be cleancut. The patients were observed with two questions in mind. The first concerned the relative therapeutic effectiveness of the specific and nonspecific horse serum globulins, and the second concerned the observation and description of the nonspecific effects in relation to the general subject of nonspecific therapy.

SUBJECTS, MATERIALS AND METHODS

Hospital cases of lobar pneumonia were studied in which the presence of type I pneumococci was determined before the end of the fourth day of the disease. The choice of specific or nonspecific therapy depended on the hospital service to which the patient was admitted, which was, in turn, entirely subject to chance. The general treatment employed in the various hospital services did not differ to any significant degree. Sixteen of the type I patients received only specific serum therapy, while thirteen received nonspecific serum therapy. Of the latter, five received only nonspecific serum therapy; eight, for whom pneumococcic type determination was completed before the end of forty-eight hours of illness, were given nonspecific therapy and were then observed long enough to judge of its complete effect, when they were given specific serum therapy. Certain characteristics of the two groups of cases which indicate that they were of similar severity are listed in table 1. They were similar in respect to the average duration of the

6. (*a*) Neufeld, F., and Haendel, L.: Weitere Untersuchungen über Pneumokokken-heilsera: III Mitteilung. Ueber Vorkommen und Bedeutung atypischer Varietäten des Pneumokokkus, Arb. a. d. k. Gsndhtsamte. **34**:293, 1910. (*b*) Cecil, R. L., and Blake, F. G.: Studies on Experimental Pneumonia: VII. Treatment of Experimental Pneumococcus Type I Pneumonia in Monkeys with Type I Antipneumococcus Serum, J. Exper. Med. **32**:1, 1920. (*c*) Goodner, Kenneth: Further Experiments with the Intradermal Pneumococcus Infection in Rabbits, J. Exper. Med. **48**:413, 1928.

7. Howard, Campbell P.: The Diagnosis and Treatment of Pneumonia, Oxford Monographs on Diagnosis and Treatment, New York, Oxford University Press, 1931, vol. 10.

8. Sutliff, W. D., and Finland, M.: Type I Lobar Pneumonia Treated with Concentrated Pneumococcic Antibody (Felton), J. A. M. A. **96**:1465 (May 2) 1931.

disease before admission to the hospital, the incidence of positive blood cultures and the development of complications, but the patients who received only specific serum therapy had a slightly higher average age owing to the inclusion of two patients of more than 50 years of age and showed a greater incidence of alcoholism. Two patients in each group died.

Two varieties of nonspecific concentrated horse serum were used. One was prepared from antimeningococcic serums by the antitoxin and vaccine laboratory of the Massachusetts Department of Public Health and furnished through the courtesy of Dr. Benjamin White. The second was a concentrated solution of normal horse serum globulin, which was prepared and furnished through the courtesy of Dr. L. D. Felton of the department of preventive medicine and hygiene, Harvard Medical School. Type-specific concentrated antipneumococcic serums were furnished by the antitoxin and vaccine laboratory of the Massachusetts Department of Public Health. The methods of preparation were, in each case, those used in the concentration of antipneumococcic serum as described by Felton,[9] with the exception of a lot of antipneumococcic serum and a lot of antimeningococcic serum that were concentrated according to the method of Goodner.[10] The protein content of the solutions of normal horse serum globulin,

TABLE 1.—*Severity of Type I Lobar Pneumonia in Two Groups of Patients Receiving Different Therapy*

	Number of Patients	Average Duration on Admission, Hours	Positive Blood Cultures on Admission	Number with Empyema	Average Age, Years	Number of Cases with Chronic Alcoholism
Specific therapy....	16	55	8	1	34.5	7
Nonspecific therapy	13*	54	7	1	30.0	2

* Includes the eight patients subsequently given specific therapy.

calculated from the nitrogen content, varied from 39 mg. to 84 mg. per cubic centimeter; of the antimeningococcic serum globulin, from 54 mg. to 82 mg. per cubic centimeter, and of the antipneumococcic serum globulin, from 76 mg. to 100 mg. per cubic centimeter.

The globulin from normal horse serum was administered to four patients, and the globulin from antimeningococcic serum was administered to nine patients, with similar results. The nonspecific serums tended to produce immediate circulatory and respiratory symptoms which, while transitory and apparently harmless, were occasionally severe. The symptoms were flushing of the face, dyspnea and a sense of compression of the chest. In only a single patient was there such an immediate reaction following the administration of specific therapy. Chills were also more frequent following the nonspecific serum, occurring in seven of thirteen cases, whereas they followed the use of antipneumococcic serum in only seven of twenty-four cases. Serum sickness of the delayed variety occurred in varying frequency according to the total amount of horse serum given—once in four recovered patients who received only nonspecific serum; three times in fourteen recovered patients who received specific serum, and five times in seven patients who received both specific and nonspecific serum.

9. Felton, L. D.: The Concentration of Antipneumococcus Serum, J. A. M. A. **94**:1893 (June 14) 1930.

10. Goodner, Kenneth: Experiments on the Concentration of Antipneumococcic and Antimeningococcic Horse Serum, J. Immunol. **19**:473, 1930.

Dosage and methods of administration that have been successful in the administration of type I antipneumococcic serum in the past [8] were used. The nonspecific serum was given as nearly as possible according to the same plan as specific serum. An arbitrary total amount, thought to be sufficient for maximum clinical effect, was given in divided doses by means of dry, sterile syringes, intravenously at two hour intervals, beginning with 5 cc. and increasing to 50 cc. The later in the course of the disease the treatment was begun, the more serum was considered necessary for symptomatic relief. A total of 30 cc. was given to patients treated within the first twenty-four hours of the disease, and for each additional day of illness before treatment was begun this dose was increased by 30 cc. The total dosage of nonspecific serum tended to be lower than that of specific serum, because, when the same patient received both varieties of therapy, the specific serum was given later, and consequently in larger amount. Furthermore, in certain patients the calculated dosage of nonspecific serum was curtailed because of the occurrence of reactions. The dosage of the nonspecific serum varied from 32 to 178 cc., with an average of 71 cc.; the specific serum, from 5 to 170 cc. with an average of 112 cc., and the specific serum given to patients who had already had nonspecific serum, from 117 to 340 cc., with an average of 162 cc. With the exception of a patient who received only 5 cc. of specific serum and who had what appeared to be a spontaneous crisis at about the time serum was begun, all the patients received at least 30 cc. of each type of serum.

RESULTS

It has been shown [8] that in lobar pneumonia observation of the symptomatic response is a simple and straight-forward method of judging the effect of serum therapy. The duration of the acute disease, the presence and alterations in bacteremia and the occurrence of extensions of the consolidation in the lungs were studied in relation to the intravenous administration of solutions of horse serum globulin with and without specific antibodies. In comparing the duration of the disease in relation to therapy, only cases in which the patients recovered were considered. In the cases in which purulent complications or serum sickness developed it was possible in all but one patient, who received both nonspecific and specific serum, to recognize a symptom-free interval marking the end of the acute disease before the second febrile attack. The data for this patient were omitted from the comparative figures of the duration of the acute disease. The effects of treatment on the blood culture and on the extent of pulmonary involvement were compared in those who died as well as in those who recovered.

Duration of the Disease.—Differences between the effect of nonspecific and specific serum on the duration of the disease were noted in the first few patients treated. It was subsequently found possible to administer, first, nonspecific serum with only temporary effect and, later, specific serum with marked permanent response. An example of such a case is illustrated by the following case report.

REPORT OF A CASE

History.—The patient, H. C., a married white woman, aged 36, was admitted on Dec. 16, 1931. She complained of sudden chill, pain on the right side of the chest and fever twelve hours before admission to the hospital. The past history was irrelevant, except for a mild chronic cough of many years' duration, with asthma in the winter, influenza and pneumonia fourteen years before admission and dry pleurisy in the left side of the "chest" one month before the present writing. She was five months pregnant.

The initial chill lasted about two hours. Generalized pains, headache, weakness, nausea and vomiting appeared.

Physical Examination.—The patient was acutely ill and in great pain; she was dyspneic and breathed rapidly. Her teeth were carious; the right tonsil was hypertrophied. Signs of consolidation were present over the lower lobe of the right lung. A loud friction rub was present in the right axilla. The patient's sputum was moderate in amount, despite the frequent coughing, and was glairy and mucoid in appearance.

Laboratory Findings.—The urine contained a slight trace of albumin. Blood counts on the day after admission showed 3,700,000 red corpuscles and 27,500 white corpuscles per cubic millimeter. The patient's sputum at this time was found to contain type I pneumococcus. Blood cultures showed no growth on the first day of illness, pneumococcus type I, on the third day and no growth on the fifth day.

Roentgen Examination.—Central consolidation of the lower lobe of the right lung was found.

Treatment and Course.—Thirty hours after the onset of the illness antimeningococcic serum therapy was begun, and 74 cc. was administered within seven hours. Reactions occurred after each dose of serum, characterized by mild nausea and dyspnea, and a chill after each of the two doses of 30 cc. The temperature fell from 103 to 98 F.; the pulse rate, from 120 to 90 beats a minute, and the respiratory rate, from 40 to 25 a minute. The temperature and pulse rate returned to 104 F. and 135 beats a minute, respectively, within twenty-four hours after the last dose of nonspecific serum. The blood culture, which had been negative on admission to the hospital, showed Pneumococcus, type I, at that time. Specific antipneumococcic serum therapy was begun, and 102 cc. was given in the course of twenty hours. Immediate reactions similar to those that occurred after the nonspecific serum were observed. The temperature returned to normal after the administration of 43 cc. of specific serum, and a permanent subjective change for the better, with relief of acute symptoms, such as dyspnea, pleural pain, marked cough and vomiting, occurred. A blood culture taken two days later, or four days after illness began, was negative. Mild serum sickness, characterized by fleeting pains in the joints and urticaria, appeared on the fifth and sixth days after the last dose of serum. Convalescence was uneventful.

This case history illustrates the dosage of serum given to patients receiving both nonspecific and specific therapy. Chart 1 shows the data for this case and also demonstrates the method of analyzing the duration of the acute disease in relation to the temperature curve. The first sustained drop of the temperature (*C*) was chosen as the point at which the temperature fell below, and later remained below, 101 F. Complete symptomatic improvement (*D*) implied that the temperature remained below 100 F., and that all symptoms of the acute disease were absent.

The most significant observation in this case was that while a temporary symptomatic improvement occurred following the administration of nonspecific serum, a marked and permanent change occurred following specific therapy. The marked contrast between the temporary symptomatic effect of nonspecific serum and the lasting effect of specific antipneumococcic serum was observed with greater or less clarity in all of the seven patients in whom the comparison was made.

The duration of the illness in relation to the administration of nonspecific or specific serum in the patients who recovered is shown in charts 2 and 3. Since the duration of the disease at the time therapy is begun modifies the effectiveness of specific therapy, it is necessary to compare patients treated in the same stage of the disease. For this

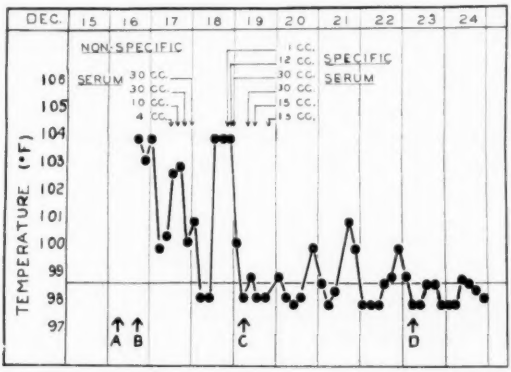

Fig. 1.—Temperature chart of patient H. C., who had type I lobar pneumonia, indicating dosage of serum and duration of disease. *A*, onset of pneumonia; *B*, entrance to hospital; *C*, first sustained drop in temperature, and *D*, complete symptomatic improvement.

purpose there were available thirteen patients who recovered and received only specific therapy and ten patients who recovered and received nonspecific therapy during the first four days of the disease. In seven of the latter patients the duration of the disease was modified by the subsequent administration of specific serum, but the contrast between the duration of the disease in the two groups is still marked. The relationship of the administration of serum to the first sustained sharp drop in temperature is indicated in chart 2. The duration of the disease up to the appearance of complete symptomatic improvement is shown in chart 3. The marked and regular effect of specific therapy in shortening the acute disease and the lack of effect of nonspecific therapy are indicated in both of these charts. The patients who received only specific therapy showed a cessation of the acute symptoms of the

disease at a short and fairly regular interval after its administration. The patients who received first nonspecific and later specific therapy recovered from their acute illness at a regular, but longer interval after the administration of nonspecific serum. The patients who received only nonspecific serum and recovered had acute symptoms for variable periods. In two of these three patients the acute symptoms lasted longer than in any of the specifically treated patients.

The average duration of the acute disease in patients who recovered also demonstrates the effectiveness of specific therapy and the ineffec-

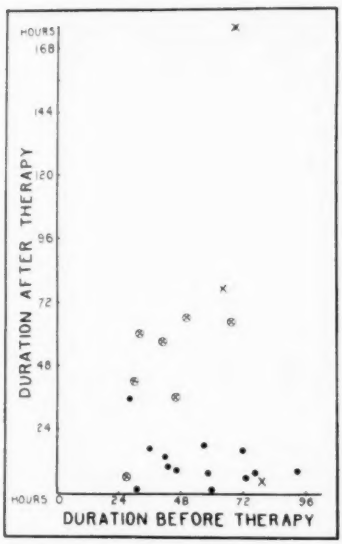

Figure 2

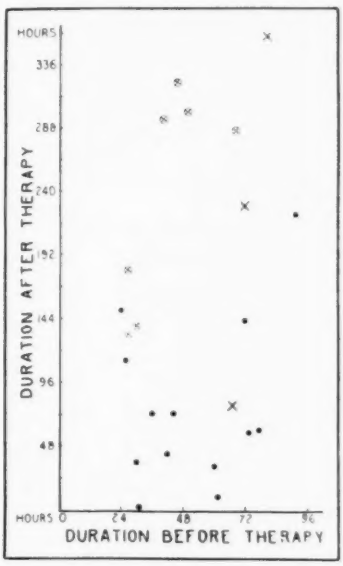

Figure 3

Fig. 2.—Relationship of therapy to first sustained drop in temperature. In this and figure 3 each cross represents a patient treated with nonspecific serum; a cross within a circle, a patient receiving first nonspecific serum and then specific serum, and each circle, a patient receiving only specific serum.

Fig. 3.—Relationship of therapy to complete symptomatic improvement.

tiveness of nonspecific therapy. The average duration of the disease before admission to the hospital was thirty-one hours for the patients specifically treated and thirty-five hours for those nonspecifically treated, and the average duration of the disease before treatment was begun was fifty-three and fifty-one hours, respectively. On the contrary, the average duration up to the first sustained drop in temperature was sixty-four

hours for patients specifically treated and one hundred and eighteen hours for those nonspecifically treated. This contrast is also evinced by the fact that the average duration up to the disappearance of all acute symptoms was one hundred and thirty-seven hours for those specifically treated and two hundred and eighty hours for those nonspecifically treated. It seems probable that had no specific therapy been subsequently given to seven of the patients treated with antimeningococcic horse serum globulin, the average duration of the condition in the patients nonspecifically treated would have been still longer.

BACTEREMIA

No effect of specific therapy in lobar pneumonia has been more striking than that exerted on the bacteremia. The patients treated here showed a fairly high incidence of bacteremia, which was similar in the

TABLE 2.—*Results of Therapy*

	Blood Culture After Therapy					
	Nonspecific Therapy			Specific Therapy		
Blood Culture Before Therapy	Number of Patients	Number Negative	Number Positive	Number of Patients	Number Negative	Number Positive
Positive	7	2	5*	11	10†	0
Negative	6	3	3	13	9‡	0

* One patient had a temporary negative blood culture after nonspecific therapy.
† One patient had no blood culture made after therapy.
‡ Four patients had no blood culture made after specific therapy; in one because of early death and in three because of recovery.

two groups. The effect of therapy is summarized in table 2. The nonspecific globulin solution had no effect on bacteremia comparable to that of the specific serum, which in every case permanently removed the bacteria from the blood. In patients who had no bacteremia before treatment, organisms later appeared in the blood in three of the patients nonspecifically treated, but did not appear in the blood of any patients specifically treated. It is worthy of note that pneumococci disappeared from the blood in three of the patients receiving nonspecific serum; in two permanently, and in one for only a few hours. The same phenomenon has been observed occasionally in this hospital following the intravenous administration of dextrose solution, and is known to occur temporarily after transfusions of blood. It is possible that this was a mere coincidence, as bacteremias undergo fluctuations that are unassociated with therapy; but the further possibility that nonspecific injections may have a regular but temporary effect in lowering the bacterial content of the blood, as has been shown by Goodner [6e] in rabbits, must be borne in mind.

EXTENSION OF THE PULMONARY CONSOLIDATION

A spread of the pneumonic lesion that was sufficiently marked to be confirmed by roentgen examination was sought in every case as an indication of prognosis and of the effectiveness of therapy. In none of the patients receiving specific therapy was a spread observed, but in five of the thirteen patients receiving nonspecific therapy such an extension was seen.

COMMENT

Previous studies of antipneumococcic serum therapy have been controlled by the simultaneous observation of patients who received no intravenous injections. The control patients whose cases are reported here were given solutions of horse serum globulin intravenously that were similar to antipneumococcic serum, except for the absence of type-specific antibodies, and the symptomatic effects achieved by the two different therapeutic materials were so consistent that the study of even a small series provided adequate data for comparison. A control was thus provided for the nonspecific actions which follow the use of specific antipneumococcic serum, but which cannot otherwise be separated from the specific effects for purposes of observation. Comparisons were made not only in different patients, but also in the same patients. They indicate that the significant symptomatic effects of serum therapy in type I lobar pneumonia depend on the presence of type-specific antibodies.

There were, however, certain symptomatic changes that followed the intravenous administration of the horse globulin that did not contain antibodies, namely, a sensation of well-being, a drop in temperature, sometimes critical in degree and abruptness, a fall in pulse rate and an occasional disappearance of bacteremia. All these changes were of short duration.

A review of previous observations on nonspecific protein therapy of lobar pneumonia shows that the symptomatic benefits are most frequently described in terms that suggest the temporary effects mentioned. Miller [1] reported the results of the treatment of fifteen patients with typhoid vaccine intravenously, noted three cases in which treatment led to a termination of the acute disease and observed temporary benefit in a number of other cases. Hiss and Zinsser,[11] in eight patients treated with leukocyte extracts, reported temporary symptomatic benefit, which was ascribed to nonspecific protein effects. Hallermann and Kähler,[3] using normal horse serum and von den Velden,[2] using normal human

11. Hiss, P. H., and Zinsser, Hans: Experimental and Clinical Studies on the Curative Action of Leukocyte Extracts in Infections, J. M. Research **14**:321, 1908.

serum and other serums containing small amounts of antipneumococcic antibodies, noted temporary effects in a small series of cases.

From what is now known of the need for potent homologous serums administered intravenously in large doses, it seems probable that many of the early attempts at specific serum treatment were more nonspecific than specific. From the work of Klemperer,[12] in 1892, to that of Neufeld and Haendel,[13] in 1910, which called attention to the different types of pneumococci, antipneumococcic serums of unknown type and of unmeasured potency were used. Goldsborough, [14] writing in 1902, lists sixty-three authors who treated a total of 486 patients. While many of these authors used small doses and administered the serum intramuscularly, some gave doses as high as 20 cc. intravenously. Temporary symptomatic effects were frequently mentioned. Later authors, who appreciated the importance of securing potent specific serum and administering large amounts intravenously, frequently did not determine the type of infection, and consequently treated many patients nonspecifically. Weitz,[15] Reuss,[16] Géronne,[17] Sonnenfeld [4] and Lichtenstein [5] have thus reported on patients treated with type-specific serum, prepared according to the directions of Neufeld and Haendel. Another group of untyped cases, in which the patients were treated with antipneumococcic serums furnished by the Pasteur Institute, have been reported by Weill-Hallé, Weissman-Netter and Aris,[18] d'Oelsnitz, Duplay and Carcopino,[19] Courcoux and Deglaire,[20] Etienne and Braun [21]

12. Klemperer, G.: Kritischer Bericht über Zwanzig Fälle spezifisch behandelter Pneumonie, Wien. med. Wchnschr. **42**:882, 1892.

13. Neufeld, F., and Händel, L.: Ueber Herstellung und Prüfung von Antipneumokokkenserum und über die Aussichten einer spezifischen Behandlung der Pneumonie, Ztschr. f. Immunitätsforsch. u. exper. Therap. **3**:159, 1909.

14. Goldsborough, Brice W.: A Contribution to the Treatment of Pneumonia with Antipneumococcic Serum, J. A. M. A. **38**:1681 (June 28) 1902.

15. Weitz, W.: Ueber die Behandlung der Pneumonie mit intravenösen Injektionen des Neufeld-Händelschen Pneumokokkenserums, Med. Klin. **8**:1072, 1912.

16. Reuss, A.: Beiträge zur Behandlung der Pneumonie mit dem Neufeld-Händelschen Pneumokokkenserum, Deutsche med. Wchnschr. **40**:1104, 1914.

17. Géronne, A.: Die Behandlung der Pneumonie mit dem Neufeld-Händelschen Pneumokokkenserum, Berl. klin. Wchnschr. **49**:1699, 1912.

18. Weill-Hallé, B.; Weissman-Netter, R., and Aris, P.: Pneumonies et broncho-pneumonies des vieillards, traitées par le serum antipneumococcique, Bull. et mém. Soc. méd. d. hôp. de Paris **46**:227, 1922.

19. d'Oelsnitz, Duplay and Carcopino: La sérothérapie des pneumopathies aigues. Bull. et mém. Soc. méd. d. hôp. de Paris **46**:588, 1922.

20. Courcoux and Deglaire: Traitement des pneumopathies aigues a penumocoques par la sérothérapie, Bull. et mém. Soc. méd. d. hôp. de Paris **46**:248, 1922.

21. Etienne, G., and Braun, M.: Sérothérapie antipneumococcique, Bull. et mém. Soc. méd. d. hôp. de Paris **47**:1813, 1923.

and Lassance.[22] The majority of these authors have felt that some temporary relief was obtained, and many described the sense of well-being and the drop in temperature and pulse rate as marking a temporary symptomatic change.

Such temporary symptomatic effects have been presented as evidence of a definite therapeutic action of serum injections in lobar pneumonia. It is apparent that they were similar to the nonspecific effects seen in the cases reported in this paper. A number of the authors mentioned felt that the death rates in their series of cases were lower than the general death rate from the disease, but owing to the lack of an adequate control mortality rate and to the small number of patients treated, these statements are open to question. The proportion of fatalities observed in "alternate case" controlled series of cases of pneumonia, as reported by Cecil and Sutliff [23] and by Finland,[24] indicates that in addition to the non-type-specific symptomatic effect there may exist a non-type-specific curative action of horse serum, since the fatality rate of pneumonia due to group IV pneumococci was less among patients who received serum containing antibodies for types I and II than among those who did not receive serum. This reduction in mortality, which was not so great as the reduction in mortality in cases of type I pneumonia reported by the same authors, was not observed by Park, Bullowa and Rosenblüth,[25] who reported the treatment of a comparable series of cases. The failure of the attempt reported in this paper to produce permanent symptomatic effects by means of nonspecific therapy in type I pneumonia would seem to indicate that the curative action of nonspecific therapy in the two series of cases of group IV cases just referred to might be questioned. It is possible that cross-protective antibodies are sometimes present [26] for organisms of the miscellaneous group IV, or that errors were made in typing of the pneumococcus which tended to the inclusion of an occasional organism of type I or II in the heterogeneous group IV.[27]

22. Lassance, V.: Le traitement de la pneumonie par le sérum antipneumococcique, Presse méd. **27**:30, 1919.

23. Cecil, R. L., and Sutliff, W. D.: The Treatment of Lobar Pneumonia with Concentrated Antipneumococcus Serum, J. A. M. A. **91**:2035 (Dec. 29) 1928.

24. Finland, M.: The Serum Treatment of Lobar Pneumonia, New England J. Med. **202**:1244, 1930.

25. Park, W. H.; Bullowa, J. G. M., and Rosenblüth, M. B.: The Treatment of Lobar Pneumonia with Refined Specific Antibacterial Serum, J. A. M. A. **91**: 1503 (Nov. 17) 1928.

26. Kolchin, Betty S., and Gross, Louis: Observations on the Cross-Protective Power of Antipneumococcus Monovalent Sera, Types I, II, and III, J. Immunol. **9**:505, 1924.

27. Sutliff, W. D.: An Investigation of the Reliability of Sputum Typing for Pneumococcus by Mouse Method, J. Infect. Dis. **42**:485 (May) 1928.

The mechanism of the action of nonspecific therapy has been discussed by Petersen,[28] by Zinsser,[29] and by Weichardt.[30] The changes that have been observed to occur following the parenteral injection of foreign protein are widespread in the body. They consist of changes in the circulating antibodies, a shift of leukocytes to the splanchnic region together with a reciprocal dilatation and contraction between the cutaneous and the splanchnic capillaries, increased permeability of the capillaries, increased flow of lymph and changes in blood serum proteins, fibrinogen and enzymes. Changes in the local inflamed area, such as dilatation of the capillaries, with resulting increased blood flow and freer exchange of antibodies and of toxic products between the lesion and the circulation also occur. These effects are all temporary and variable. They probably account together or separately for the temporary symptomatic changes that were noted in the nonspecific treatment in the cases here reported.

SUMMARY

A comparison has been made between the symptomatic effects obtained in early type I lobar pneumonia by the administration of concentrated type-specific antipneumococcic serum and of horse serum globulin solution containing no specific antipneumococcic antibodies. Both preparations were prepared and administered in the same manner.

In eight patients who received, first, nonspecific and, later, specific therapy, the greater effectiveness of the latter was obvious.

In thirteen specifically treated patients who recovered the duration of the disease was shorter than in the ten nonspecifically treated patients who recovered.

Bacteremia was not present after therapy in any of the sixteen specifically treated patients, but bacteremia remained present in five, appeared for the first time in three and disappeared in two of thirteen nonspecifically treated patients.

An extension of the consolidation of the lung was not observed after therapy in any of the sixteen specifically treated patients, but extensions were observed in five of thirteen patients receiving nonspecific therapy.

A temporary symptomatic change was observed in each of the patients receiving nonspecific therapy, but the improvement in patients receiving specific therapy was permanent in every instance.

---

28. Petersen, W. F.: Protein Therapy and Non-Specific Resistance, New York, The Macmillan Company, 1922.

29. Zinsser, Hans: Resistance to Infectious Disease, ed. 4, New York, The Macmillan Company, 1931, p. 470.

30. Weichardt, W.: Unspecifische Immunisierung, in Kolle, W.; Kraus, R., und Uhlenhuth, P.: Handbuch der pathogenen Mikroorganismen, ed. 3, Jena, Gustav Fischer, 1931, vol. 1, p. 1147.

NEPHRITIC ALBUMINURIA

J. M. HAYMAN, JR., M.D.
AND
J. A. BENDER, M.D.
CLEVELAND

Since the time of Bright, albuminuria has commonly been associated with disease of the kidneys. More recently the distinction has been made between non-nephritic and nephritic albuminuria. The former is most readily attributed to a transient and reversible increase in permeability of the glomerular membrane from partial asphyxia brought about by circulatory changes.[1] From time to time, however, the suggestion has been made that nephritic albuminuria is the result of changes in the plasma proteins rather than any change in or damage to the kidney itself. Epstein [2] saw in the albuminuria of nephrosis a disturbance of plasma protein formation; Kollert and Starlinger [3] an increased tissue destruction leading to increase in fibrinogen; and Munk and his associates,[4] an abnormality in the physicochemical state of the plasma colloids. The conception of extrarenal albuminuria is supported by the appearance of foreign proteins, such as egg albumin, in the urine after ingestion of large quantities, or after their intravenous injection. The albuminuria following the injection of foreign protein, however, is usually transitory and without evidence of lasting damage to the kidneys. Hamburger [5] found that with repeated injections of egg white the albuminuria decreases and even disappears, the kidney cells having become immune to the foreign protein. Garnier and Schulmann [6] have made similar observations.

From the Department of Medicine of the Western Reserve University and Lakeside Hospital.

1. Starr, Isaac, Jr.: The Production of Albuminuria by Renal Vasoconstriction in Animals and Man, J. Exper. Med. **43**:31 (Jan.) 1926.

2. Epstein, A. A.: Thyroid Therapy and Thyroid Tolerance in Chronic Nephrosis, J. A. M. A. **87**:913 (Sept. 18) 1926.

3. Kollert, V., and Starlinger, W.: Ueber das Verteilungsverhältnis der Eiweisskörpergruppen des Blutplasmas und Harnes bei Nierenkranken, Ztschr. f. klin. Med. **104**:44, 1926.

4. Munk, F.; Benatt, A., and Flockenhaus, M.: Experimentelle Untersuchungen über das Wesen der Albuminurie und der Lipoidnephrose, Klin. Wchnschr. **4**:863 (April 30) 1925.

5. Hamburger, F.: Zur Frage der Immunisierung gegen Eiweiss, Wien. klin. Wchnschr. **15**:1188, 1902.

6. Garnier, M., and Schulmann, E.: Sur l'albuminurie déterminée par l'injection de blanc d'oeuf au lapin, Compt. rend. Soc. de biol. **93**:600 (July 25) 1925.

Andrews, Thomas and Welker[7] have suggested that albuminuria may be regarded as a method of detoxication of the body. Their conception is that a disturbance in the ratios of inorganic salts in the body allows proteins to escape from tissue cells which are foreign to the blood stream and are therefore excreted by the kidney, either alone or in combination with the plasma proteins, which because of such combination are themselves changed to foreign proteins. If such were the case, it seemed to us that plasma from nephritic patients who were excreting large amounts of protein should, when injected into a normal person, lead to the appearance of albuminuria.

We have, therefore, injected from 50 to 190 cc. of citrated plasma from three such patients who had negative Wassermann reactions and no history or evidence of syphilis, into persons of compatible blood groups who had no albuminuria or detectable renal damage. In no case was albuminuria produced. Brief histories of the cases follow.

REPORT OF CASES

CASE 1.—The clinical diagnosis was chronic nephritis with edema. The pathologic diagnosis four months later (Dr. H. T. Karsner) was: borderline case; no clearcut anatomic distinction between arteriolar nephrosclerosis and chronic nephritis.[8]

---

7. Andrews, E.: Experimental Uremia, Arch. Int. Med. **40**:548 (Oct.) 1927. Andrews, E., and Thomas, W. A.: The Origin of Urinary Proteins, J. A. M. A. **90**:539 (Feb. 18) 1928. Andrews, E.; Thomas, W. A., and Welker, W. F.: Albuminuria in the Mechanism of Detoxification, Arch. Int. Med. **43**:139 (Jan.) 1929.

8. The kidneys grossly showed no distinct reduction in size but slight pitting of the surface. They were principally the seat of passive hyperemia. Microscopically, the capsule was absent. The surface showed numerous areas of depression at the base of which was a triangular area of fibrosis with lymphoid cell infiltration. The elevated portions showed small cystlike dilatations of the tubules. The connective tissue generally was slightly increased in amount and moderately edematous. The tubular epithelium and the subcapsular epithelium showed advanced cloudy swelling. Fat stains showed well marked fatty degeneration in both situations. Polarizing prisms failed to disclose anisotropic droplets. A few hyaline casts were present. The large and medium-sized arteries showed moderate intimal fibrosis. The small arteries showed marked intimal and medial fibrosis with only slight fatty changes. The arterioles in some places showed thick and fibrotic walls, but with only slight fatty changes. The glomeruli varied greatly in size, but those that were not markedly fibrotic were unusually large. Fibrosis attacked both the capsule and the tuft, and in numerous instances there was complete replacement of glomeruli by fibrous and fibrohyaline material. The larger tufts showed well marked lobulation and many blood-containing loops, appeared to be richly cellular and often showed adhesions between the tuft and the capsule. Variable degrees of fibrosis with slight hyaline change were found in the tufts, and occasionally a loop was completely hyalinized. The Azan-Carmine stain of McGregor showed considerable thickening of the basement membrane with only a few areas in which it was wrinkled. There were, then, severe chronic

E. R., a Hungarian woman, aged 54, was admitted to the hospital on June 9, 1930, complaining of swelling of the legs and abdomen of nine months' duration, and of the arms and trunk for one month. Physical examination revealed no dyspnea, but marked pallor. There were marked sclerosis of the retinal arteries, many hemorrhages and patches of exudate. The lungs were normal except for a few râles at the bases. The heart was enlarged; the blood pressure was 230 systolic and 130 diastolic, falling to 170 systolic and 90 diastolic with rest. There was marked peripheral arteriosclerosis. The abdomen contained a moderate amount of fluid. The liver was not demonstrably enlarged. There were marked edema of the legs, and less of the arms and trunks. The volume of urine secreted was from 300 to 900 cc. a day; the specific gravity was from 1.020 to 1.032; the protein content was from 2 to 9 Gm. daily computed by Esbach's method; three estimations of protein nitrogen by Kjeldahl's method showed 6.4, 8 and 8.4 Gm.; there were many hyaline and granular casts, and no red cells. The blood count showed 4,000,000 erythrocytes; hemoglobin, 600 per cent (Sahli), and 8,000 leukocytes. The blood urea nitrogen was 15 mg., creatinine 1.6 mg. and cholesterol 240 mg., per hundred cubic centimeters. The total plasma proteins were 4.3 Gm. per hundred cubic centimeters. The Wassermann test was negative.

On August 2, 100 cc. of blood was drawn into a flask containing 10 cc. of 2 per cent sodium citrate; the plasma was separated under sterile precautions, and 50 cc. was injected intravenously into a healthy subject. There were no symptoms or reaction of any kind. Each specimen of urine voided by the recipient during the following twenty-four hours was tested qualitatively for protein with heat and acetic acid and with nitric acid. None gave a detectable reaction.

CASE 2.—The diagnosis was subacute nephritis.

L. L., a 17 year old Negress, was admitted to the hospital on Nov. 16, 1931, complaining of swelling of the face and ankles of five months' duration. Physical examination gave essentially normal results, except for edema of the lower lids and pitting edema of the ankles and legs and over the sacrum. The volume of urine was from 600 to 2,100 cc. a day; the specific gravity was from 1.014 to 1.030; the albumin (Shevky and Stafford's[9] method) was from 6.7 to 7.3 Gm. a day; there were a moderate number of erythrocytes and many hyaline and granular casts. The blood count showed: 4,700,000 erythrocytes; 65 per cent hemoglobin (Sahli); 7,800 leukocytes. The test for phenolsulphonphthalein showed 60 per cent. The blood urea nitrogen was 12 mg. per hundred cubic centimeters. The total plasma proteins were 5.3 Gm. per hundred cubic centimeters. The Wassermann test was negative. Roentgen examination showed clouding of both antrums.

On January 2, 300 cc. of blood was drawn into a flask containing 30 cc. of 2 per cent sodium citrate. The plasma was separated under sterile precautions and 190 cc. was injected intravenously into a healthy man whose blood showed no cross-agglutination with that of the patient. Thirty minutes after the injection urticarial wheals developed which were relieved by epinephrine. The recipient's urine showed no protein by qualitative test either before or after injection, nor could any increase in excretion of protein be detected by Shevky and Stafford's

---

arterial and moderate arteriolar lesions, glomerular changes that were somewhat more like those of inflammatory than like those of arteriolar disease and a marked simple nephrotic component evident in the advanced cloudy swelling and fatty degeneration of the tubules.

9. Shevky, M. C., and Stafford, D. D.: A Clinical Method for the Estimation of Protein in Urine and Other Body Fluids, Arch. Int. Med. **32**:222 (Aug.) 1923.

quantitative method either in the specimen voided an hour after injection or in those obtained during the following forty-eight hours.

CASE 3.—The diagnosis was chronic nephrosis.

J. T., a white man, 21 years of age, was admitted to the hospital on May 26, 1932, complaining of generalized edema and swelling of the abdomen of six months' duration. Physical examination showed marked pallor and generalized edema involving particularly the legs, the lower part of the trunk and the scrotum. The eyegrounds were normal; the lungs were apparently normal. The heart was not enlarged to percussion; the blood pressure was 130 systolic and 90 diastolic; the peripheral vessels were soft. The abdomen contained a moderate amount of fluid. The volume of urine was from 450 to 1,400 cc. a day; the specific gravity was from 1.014 to 1.038; the albumin was from 19 to 33.3 Gm. a day (Shevky and Stafford's method). The sediment showed many hyaline and granular casts and no red cells on ordinary examination. An Addis count showed: red cells 616,000; white and epithelial cells, 53,000,000, and casts, 20,000,000, per twelve hours. There was 25 per cent excretion of phenolsulphonphthalein after intravenous injection. The blood urea nitrogen was 27.6 and the cholesterol, 477 mg. per hundred cubic centimeters. The total plasma protein was 4.3 mg. The blood count showed: 4,000,000 erythrocytes, 80 per cent hemoglobin and 9,400 leukocytes. The basal metabolism rate was —13 per cent. The Wassermann test was negative.

On May 25, 400 cc. of blood was drawn into a flask containing 40 cc. of 2 per cent sodium citrate, the plasma separated under sterile precautions and 175 cc. injected intravenously into a healthy man whose blood showed no cross-agglutination with that of the patient. There was no reaction of any kind. The recipient's urine gave no qualitative test for protein before or after injection. By Shevky and Stafford's method, the concentration of protein in the recipient's urine for twenty-four hours before injection was approximately 0.006 mg. per hundred cubic centimeters; for the twenty-four hours after injection, it was the same.

The question naturally arises whether the amount of plasma injected contained enough foreign protein to be detectable even if it were excreted. This is difficult to answer definitively. In case 3, the daily protein in the urine was usually in excess of 20 Gm. Assuming the plasma volume to be 5 per cent of the body weight (73 Kg.), the total plasma volume would be about 3.65 Kg., or approximately 3,360 cc. The total plasma proteins were 4.3 per cent, making a total of about 145 Gm. in the blood stream. The patient was thus excreting the equivalent of about one seventh of his total plasma proteins a day. If a similar ratio is assumed for the plasma transfused, about 1 Gm. of the 7.53 Gm. of protein injected would have been excreted if it had stayed in the patient's vessels. The method used for detecting protein could easily be read to 0.015 mg. per hundred cubic centimeters (or about 0.15 Gm. in a twenty-four hour volume of urine). Therefore, if one sixty-seventh of the protein excreted by the patient, or one five hundredth of the plasma proteins injected, represented foreign proteins, we believe that we could have detected it, provided all of it were promptly eliminated by the kidney. If the excretion took place slowly during twenty-four hours, about one fiftieth of the protein injected would have to have been excreted in order to be readily detected.

These experiments may be regarded as another failure to demonstrate by direct experiment qualitative changes in the plasma proteins of persons having nephritic albuminuria. It is well established that intravenous injection of sufficient foreign protein may be followed by albuminuria, the urinary protein containing both the foreign protein and serum proteins. The amount of foreign protein excreted, however, is always less than that injected,[10] and albuminuria, when it occurs, is most readily explained by a toxic damage to glomeruli, for by no means is every intravenous injection or liberation of foreign protein in the blood stream followed by albuminuria, even when definite systemic reactions are produced. We have failed to detect protein in the urine of four patients receiving intravenous injections of from 25,000,000 to 1,600,000,000 typhoid bacilli, although in each case there was a well marked reaction characterized by chill and fever, nor have we detected it with any regularity after the chills of therapeutically induced malaria.

These experiments are consonant with the dialysis experiments of del Baere [11] and Gaebler [12] who failed to find any increased diffusibility of the plasma proteins of patients with albuminuria and are contrary to those of Andrews, Thomas and Welker.[7] A similar experiment was reported by Rusznyak and Nemeth,[13] who did not find any greater proteinuria when a dog's kidney was perfused with diluted serum from a patient with nephrosis than when normal serum was used, and concluded that albuminuria is due to alterations in the glomeruli, not in the plasma proteins. After a detailed discussion of the extrarenal factors in albuminuria, Volhard [14] concluded that "in the last analysis every albuminuria must be attributed to damage of the kidney epithelium."

CONCLUSION

Intravenous injection of plasma from three patients with nephritis who were excreting large amounts of protein did not cause albuminuria in healthy recipients. This is regarded as inconsistent with the conception that nephritic albuminuria is due to the presence of foreign toxic proteins in the blood stream.

10. Schmid, J.: Ueber den Ausscheidungsort von Eiweiss in der Niere, Arch. f. exper. Path. u. Pharmakol. **53**:419, 1905.

11. del Baere, L. J.: Die Ursache der Albuminurie bei der Nephrose, Ztschr. f. d. ges. exper. Med. **79**:743, 1931.

12. Gaebler, O. H.: Diffusibility of the Proteins of Normal and Pathological Plasma, J. Biol. Chem. **93**:467 (Oct.) 1931.

13. Rusznyak, S., and Nemeth, L.: Die Entstehung der Albuminurie, Ztschr. f. d. ges. exper. Med. **70**:464, 1930.

14. Volhard, F.: Nieren und ableitende Harnwege, in von Bergmann, G., and Staehelin, R.: Handbuch der inneren Medizin, ed. 2, Berlin, Julius Springer, 1931, vol. 6, p. 821.

SPONTANEOUS SUBARACHNOID HEMORRHAGE

A. L. OSTERMAN, M.D.
WHEELING, W. VA.

Despite characteristic and striking clinical symptoms and a not infrequent occurrence, the syndrome of spontaneous subarachnoid hemorrhage is still largely unrecognized in general practice. This fact, together with the recent observation of a case of spontaneous subarachnoid hemorrhage, has prompted a brief review of the present status of the subject and a report of the case at hand.

Subarachnoid hemorrhage, like jaundice or pruritus, is merely a symptomatic expression of some more fundamental pathologic state. Subarachnoid hemorrhage as a coincidental sign may be found in a variety of pathologic conditions. It may occur in trauma directed to the skull or vertebral column, as in fracture or dislocation, when vessels are ruptured and blood is extravasated into the subarachnoid space. It may occur in acute or chronic inflammatory processes in the meninges or encephalon, as in meningococcic, syphilitic or tuberculous meningitides or in epidemic and hemorrhagic encephalitides (vaccinia, smallpox and measles). Its occurrence has been reported in dyscrasias of the blood, such as purpura, hemophilia, scurvy and the leukemias, in which a defect in the factors of coagulation exists. Subarachnoid hemorrhage has been known to occur in such miscellaneous states as pernicious anemia, polycythemia, sickle cell anemia, Korsakoff's psychosis, migraine and vascular neurosyphilis and as a sequel to the administration of serums or vaccines. The rupture of cerebral cysts or the erosion of blood vessels by cerebral neoplasms affords other causes of subarachnoid hemorrhage. Hypertension, whether permanent, as in chronic nephritis, or transient, as in the paroxysms of eclampsia, epilepsy or pertussis, is a fruitful source of subarachnoid hemorrhage. Toxins, such as lead and alcohol, may initiate hemorrhage from the cerebral vessels into the subarachnoid reservoir.

The type of subarachnoid hemorrhage in which all the aforementioned factors, whether traumatic, infectious, toxic, neoplastic, hypertensive or dyscrasic, can be excluded as causative has been termed "spontaneous." The term "spontaneous" has been well chosen, because the hemorrhage usually makes its appearance suddenly and dramatically, without evident cause, in a person previously in apparently vigorous health. The term "spontaneous" is perhaps applied in this connection

From the Department of Internal Medicine, Wheeling Clinic.

in the same sense that it is applied in "spontaneous combustion" in the realm of chemistry. Again, the expression "spontaneous" is in no sense to be regarded as equivalent to that equivocal term "idiopathic," because in each instance of spontaneous subarachnoid hemorrhage there is a definite pathologic process. This pathologic process always consists of disease or degeneration of the cerebrospinal arteries per se.

The usual cause of spontaneous subarachnoid hemorrhage is the rupture of a congenital aneurysm or an aneurysm resulting from a congenital defect in the vessel wall. Symonds, Ohler and Hurwitz,[1] McIver and Wilson,[2] and Fearnsides have supported this view. The last named investigator reported forty-four cases of aneurysm of the cerebral arteries among 5,432 patients on whom autopsy was performed at the Pathological Institute of London Hospital between the years 1907 and 1913; of this number, the condition in thirty-one cases was due to medial degeneration and in thirteen, to embolic processes. Such aneurysms most frequently involve branches of the circle of Willis at their bifurcation and may be single or multiple.

Strangely enough, syphilis is practically never a cause of cerebral aneurysm, and hence it is not a cause of spontaneous subarachnoid hemorrhage. Fearnsides has shown that while syphilis causes 96.2 per cent of aortic aneurysms and practically all aneurysms of other vessels, it is rarely a cause of intracranial aneurysm. In the cerebral arteries syphilis causes obliterating endarteritis, but not aneurysms. Ohler and Hurwitz [1] recently reported twenty-four cases of spinal subarachnoid hemorrhage in all of which the Wassermann tests of the blood and spinal fluid were negative.

Aside from aneurysm, a few other causes of intrinsic cerebral vascular disease have produced spontaneous subarachnoid hemorrhage. Transverse rents in the internal elastic lamina of the blood vessels have been found on microscopic study. Cerebral arteriosclerosis is an occasional cause. Functional vasomotor disturbance of the cerebral vessels with extravasation of blood has been suggested in a few instances.

Symonds has rightly stated that the blood present in the spinal fluid must have its origin from one of four sources: (1) the rupture of a vessel lying in the subarachnoid space; (2) hemorrhage from a superficial cerebral vessel, with rupture through the pia mater into the subarachnoid; (3) hemorrhage from a deep cerebral vessel into the ventricles, and finally, (4) rupture from a subdural vein through the subarachnoid membrane.

1. Ohler, W. R., and Hurwitz, D.: Spontaneous Subarachnoid Hemorrhage, J. A. M. A. **93**:1856 (May 28) 1932.

2. Wilson, G., and McIver, J.: Spontaneous Subarachnoid Hemorrhage, J. A. M. A. **93**:89 (July 13) 1929.

HISTORICAL REVIEW

It is interesting to note from the historical point of view that spontaneous subarachnoid hemorrhage was not recognized clinically earlier than 1904. Prior to that time, diagnoses were made only post mortem. While Sir William Gull, in 1859, discussed the possibility of aneurysmal rupture as the cause of subarachnoid hemorrhage, Wilks in the same year actually reported four cases. Gentrae collected thirty-four cases from the literature in 1869. Froin, in 1904, by accurately describing the characteristics of admixtures of blood and spinal fluid, and Quincke, in 1891, by his invention of the lumbar puncture, established criteria and methods by means of which a diagnosis could be made ante mortem. Samuel Leopold [3] was one of the earliest investigators of the subject in American medical literature; he published an article on spontaneous leptomeningeal hemorrhage in *The Journal of the American Medical Association* in 1914.[4] Both he and Josephine Neal (1926) decried the paucity of American reports as compared with the relative frequency of cases in English, Swedish and French medical literature. Fearnsides, in 1916, recognized the cause of spontaneous subarachnoid hemorrhage as being a rupture of a congenital aneurysm in the young or arteriosclerotic degeneration in the aged. By 1924, C. P. Symonds of Guy's Hospital had collected seventy-seven references from the literature, only one case of which was from an American source. Since 1929, however, an increasing number of American investigators have reported cases, among them McIver and Wilson [2] (July, 1929), who reported fifteen cases, Smith [5] (June, 1930), Leopold [3] (January, 1930), who reported three cases, Sands [6] (July, 1930), and, finally, Ohler and Hurwitz,[1] who recorded twenty-four cases of this syndrome (May 28, 1932).

The incidence of spontaneous subarachnoid hemorrhage may be gaged by the statement of Ohler and Hurwitz that it constitutes one fifteenth of all cerebrovascular accidents and is equivalent in frequency to a better recognized clinical entity—subacute bacterial endocarditis. They reported twenty-four cases of spontaneous subarachnoid hemorrhage occurring at the Boston City Hospital in the eighteen months elapsing between June, 1929, and January, 1931. On the other hand,

3. Leopold, S. S.: Spontaneous Subarachnoid Hemorrhage, M. Clin. North America **13**:869 (Jan.) 1930.

4. Leopold, S.: Subarachnoid Hemorrhage, J. A. M. A. **63**:1363 (Oct. 17) 1914.

5. Smith, W. A.: Spontaneous Subarachnoid Hemorrhage, South. M. J. **23**: 494 (June) 1930.

6. Sands, J.: Subarachnoid Hemorrhage as a Clinical Complication of Neurosyphilis, Arch. Neurol. & Psychiat. **24**:85 (July) 1930.

S. S. Leopold reported only three cases on the medical service of the University of Pennsylvania in the year 1929.

The onset of symptoms of spontaneous subarachnoid hemorrhage is sudden, dramatic and brutal. Almost universally patients at the onset have been engaged in exertion, such as running, playing games, laughing or coughing. The case reported is the only one in the literature available to me which occurred coincidentally with the strain of intercourse. The patients frequently have been in good health and are in the fourth or fifth decade of life. The average age was only 27 years in Neal's cases and 30 years in Symonds', but in the twenty-four cases of Ohler and Hurwitz it was 50 years (the youngest being 17 years, the oldest 75 years).

The first and indeed the only symptom complained of may be violent and excruciating occipital headache of such abrupt onset that the patient may feel as if he had been "struck at the base of his skull." This headache may be associated with severe suboccipital pain. Vertigo and persistent vomiting are next most frequent symptoms. Coma or stupor may be present in larger hemorrhages. Some disorientation or mental confusion, somnolence or slowness of comprehension may coexist with the pain in the head if coma does not supervene.

Moderate elevation of temperature to between 99 and 102 F. is the rule. The highest elevation occurs the first week, when the greatest hemolysis and pigment absorption are present. Defervescence may require from ten to twelve days. Referred pains along the peripheral nerves may occasion herpes zoster or sciatic neuralgia. Objectively, very little neurologic or physical disturbance may be present. There are two fairly constant signs, a stiff, rigid neck and a positive Kernig sign. Paresis of the facial muscles or of one or more extremities may exist; the reflexes are not infrequently abolished, although they may be present or hyperactive. Pupillary findings are variable. Subretinal hemorrhages from effusion of blood along the optic nerve sheaths and choked disks have been recorded.

From the laboratory standpoint, a leukocytosis of 13,000 or 14,000 is often present. A trace of albumin or even of dextrose may occasionally be found in the urine.

A spinal fluid uniformly mixed with blood and under increased tension is a requisite finding. The blood must be present equally in three or more consecutive test tubes; it should not clot, and there should be xanthochromia of the supernatant spinal fluid for three or four hours after the accident, becoming progressively deeper the first week and ultimately clearing up in patients who recover. These criteria serve to eliminate the finding of blood in the spinal fluid from extraneous, accidental sources.

The following case report is classic:

REPORT OF A CASE

History.—E. W., a white man, aged 40, a postmaster by occupation, who had previously been in excellent health, was seen at the Glendale Hospital in consultation with Dr. Covert of Moundsville, on May 27, 1932. The patient's chief complaints were violent occipital headache and dull lumbar backache. The headache had had an abrupt, catastrophic onset at 4 p. m., Sunday, May 23, 1932, immediately after the successful performance of conjugal coitus. At the termination of the act, the patient had felt a snap in the occipital area of his head and thought that he had dislocated a vertebra, so intense was the ensuing pain. The pain or ache in the head was situated in the occipital area; it was excruciating and was referred anteriorly to each temporal area. With each heart beat, the patient had felt a paroxysmal intensification of the pain. The headache was not relieved by any of the usual measures and continued largely unabated for two days, when he was removed to the hospital. Only two measures had temporarily alleviated the pain in the head—a full warm tub bath had given relief, for half an hour; and elevation of the head had aided a trifle.

There had been no tinnitus aurium, vertigo or symptoms relative to the cranial nerves. The patient had not vomited. There had been no period of unconsciousness. However, the patient was somewhat disoriented when seen; his comprehension was dulled.

Two days after the onset, marked stiffness of the neck with actual soreness of the suboccipital muscles developed. At the same time, a dull, constant, lumbosacral backache appeared. Pains were also referred down the posterior aspects of both thighs along the course of each sciatic nerve.

The patient's past illnesses were insignificant. No history of a recent cold in the head, injury or acute infection was obtained. He had last consulted a physician eighteen months previously, and then only for a routine insurance examination. He had been feeling quite well for several years and had gained 25 pounds (11.3 Kg.) in the past four years. He said that he had not had venereal infection. The patient had been married twice. The family history was essentially unimportant.

Examination.—Complete physicial and neurologic examinations revealed a surprising lack of findings. The only positive findings were: (1) marked rigidity of the neck and soreness of the suboccipital muscles, (2) a bilaterally positive Kernig sign and (3) elicitation of slight pain along the course of the sciatic nerves in their crural extent and soreness of the posterior crural muscles.

The patient was a large, well built, slightly obese man of hypersthenic and plethoric habitus. He was obviously worried and had an anxious expression on his face. His complexion was ruddy. He was slightly confused. The blood pressure was 110 systolic and 65 diastolic; there was no evident peripheral or retinal arteriosclerosis. The temperature was 101 F.; the pulse rate was 88 a minute. The head was of normal configuration and presented no pathologic deviations. The pupils were somewhat small, but they were regular and equal and responded well to light and in accommodation, and the convergence was normal. The auditory canals and ear drums were normal, and nasal inspection gave negative results. The teeth were in good condition; the tonsils were normal and the sinuses clear on transillumination. There was no evidence of a pulmonary, pleural or cardiac pathologic condition. Abdominal, rectal and genital examinations gave negative results.

The gait was essentially normal. There was slight swaying in the Romberg position. No defect in the cranial nerves, the sensory modalities or the superficial or deep tendon reflexes was present. Cerebellar signs were absent. No abnormal associated or involuntary movements or anomalies in motor strength or muscle status were in evidence.

Lumbar puncture revealed a uniformly bloody spinal fluid under an increased pressure of 260 mm. of water. The blood was equally distributed in each of four tubes and did not clot. The red cells formed a sediment in each tube, and the supernatant fluid was xanthochromic. Other examinations of the spinal fluid gave the following data:

1. The cell count showed 32 leukocytes. 2. A differential count of leukocytes revealed: 20 lymphocytes, or 62.5 per cent, and 12 polymorphonuclears or 37.5 per cent. 3. The Pandy and Ross-Jones tests showed an increased amount of globulin. 4. The colloidal gold test was negative. 5. The Wassermann test was negative in dilutions of 0.2, 0.4 and 0.6 cc. 6. Smears were repeatedly found to be negative. 7. Cultures were repeatedly negative. 8. A quantitative test for sugar showed 48 mg. per hundred cubic centimeters. 9. A quantitative test for protein showed 60 mg. per hundred cubic centimeters.

The Wassermann and Kahn tests of the blood were negative on May 27, 1932. A typical blood count made on May 27, 1932, showed 9,800 leukocytes, with 79 per cent neutrophils, 17 per cent small lymphocytes, 2 per cent large lymphocytes and 2 per cent eosinophils. The red cell count and hemoglobin were normal. Repeated urinalyses showed no unusual observations; there were traces of indican, a slight amount of acid, a specific gravity of from 1.004 to 1.012, no sugar, no albumin, an occasional hyaline cast in one specimen, a trace of acetone in another, amorphous urates and uric acid crystals.

Course.—The patient's treatment was pursued along the following lines:

1. A lumbar puncture was made daily, with the removal of from 20 to 30 cc. of sanguineous fluid. During the first week the supernatant fluid became progressively saffron yellow; then gradually the fluid began to lose its pigment, until by the twelfth day it was practically clear. The punctures were continued until the fluid was clear and under normal tension. The punctures were the most effective single measure in relieving the pain in the head.

2. Daily intravenous injections of 500 cc. of a hypertonic 10 per cent solution of dextrose were made.

3. A saline catharsis was administered each morning.

4. Complete rest in bed with the continuous application of two ice caps to the head was given.

5. Mild analgesics were used.

The patient remained in the hospital for two weeks. His convalescence was uneventful after the first week, when the headache, backache and fever largely subsided. He was discharged on June 9, 1932, free from symptoms. He has now returned to his former work and apparently enjoys his usual health.

COMMENT AND CONCLUSION

The abrupt onset of the pain was doubtless due to the rupture of a congenital aneurysm, situated perhaps along a posterior branch of the basally placed circle of Willis. With each ventricular systole a paroxysmal intensification of the pain ensued from increased extravasation of

blood into the subarachnoid space. All of the symptoms were due to two factors (1) the increased intracranial pressure and (2) the extravasation of blood into a closed serous sac. Meningeal irritation would account for the stiff neck and the bilateral Kernig sign. The irritation of the sacral roots of the sciatic nerve, which pursue a long intrathecal course, by the blood pigment would serve to explain sacral backache and sciatic neuralgia. Finally, it must be noted that while the patient is apparently well, another aneurysmal rupture may ensue.

ORAL ADMINISTRATION OF IRON IN HYPOCHROMIC ANEMIA

CLARK W. HEATH, M.D.
BOSTON

One of the oldest problems in which modern scientific medicine has interested itself is that concerning the efficacy of iron in the treatment of anemia. Perhaps no other problem has attracted so much thought and work with results so little in agreement. This idea has been expressed well by Whipple and Robscheit-Robbins:[1] "The history of anemia treatment with drugs is indeed a tale to make the judicious grieve."

Some of the conflicting ideas regarding iron medication may be traced to the careless application of the discoveries made in experimental anemia in animals to the anemias that occur in man. For the present, until more is known of the mechanisms involved in different types of anemia, in man and animals, the statement of Witts is much to the point, namely, that no apology is needed for considering the field of clinical medicine the testing ground of iron therapy.[2]

In the past hundred years the prescribed dose of iron in anemia has varied widely. Blaud, in 1832,[3] soon after he had announced the efficacy of certain pills which he regarded as specific in the treatment of chlorosis, voiced an objection to a formula which reduced the strength of his pills to about one-half. On the whole, not only since that time, but since at least the time of Sydenham, iron was considered of great value in the treatment of chlorosis.[4] In the hands of those physicians who found it specific in this disease it was used in large doses for prolonged periods. During that century iron was often prescribed in doses that today would be considered too small. For a period in recent years it has been relegated to a minor therapeutic position, chiefly by reason of its lack of effect experimentally in acute blood loss, possibly

This study was aided in part by a grant from the Josiah Macy, Jr., Foundation.

From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital, and the Department of Medicine, Harvard Medical School.

1. Whipple, G. H., and Robscheit-Robbins, F. S.: Blood Regeneration in Severe Anemia: III. Iron Reaction Favorable, Am. J. Physiol. **72**:419, 1925.

2. Witts, L. J.: Discussion on the Therapeutic Uses of Iron, Proc. Roy. Soc. Med. **24**:543, 1931.

3. Blaud, P.: Pilules anti-chlorotiques, Bull. gén. de thérap. **2**:154, 1832.

4. Christian, H. A.: A Sketch of the History of the Treatment of Chlorosis with Iron, M. Lib. & Hist. J. **1**:176, 1903.

also because of the less frequent occurence of severe chlorosis and because of its frequent use in anemia that cannot respond to iron therapy. Recently it has been elevated once again to a position of great importance in the treatment of certain kinds of anemia. This extraordinary change in the point of view has been commented on by Whipple and Robscheit-Robbins.[1]

The different kinds of iron preparations that have been employed are as various as the different dosages recommended. In general, the activity of different iron preparations is believed to depend on the physical and chemical state of the iron which they contain [5] and on the gross amount of iron which is given in the daily dose.[6] Organic iron preparations are not as effective as inorganic preparations.[7] Reimann and Fritsch [8] found that ferrous chloride and ferrous sulphate in small doses were much more active in producing hemoglobin regeneration than the corresponding ferric salts.

Much further research is necessary before it is learned what is the best form of inorganic iron preparation to employ clinically. There are numerous simple preparations which are potent in types of cases that are known to respond to iron, if they are given in the proper dosage and for an appropriate length of time. An analysis of the important factors in eighty-four cases of hypochromic anemia due to various causes is the basis of the present report.

METHODS

As a rule, venous blood was taken every other day for complete blood studies. The percentage of reticulocytes was determined daily on capillary blood during the first few weeks of treatment. Subsequently, when the hemoglobin reached a level of over 60 per cent of normal and the patient had left the hospital, the hemoglobin and the number of red blood corpuscles were determined at about monthly intervals.

The hemoglobin was determined by the Sahli hemometer, which had been standardized by determinations of the oxygen capacity of the blood by the Van Slyke apparatus. One hundred per cent hemoglobin was taken as the equivalent of 15.6 Gm. per hundred cubic centimeters of blood, or 21 per cent by volume of oxygen capacity. The blood counts were made with United States Bureau of

5. Morawitz, P.: Ueber Eisen- und Arsenpräparate, München. med. Wchnschr. **71**:1266, 1924.

6. (*a*) Mettier, S. R., and Minot, G. R.: The Effect of Iron on Blood Formation as Influenced by Changing the Acidity of the Gastroduodenal Contents in Certain Cases of Anemia, Am. J. M. Sc. **181**:25, 1931. (*b*) Keefer, C. S.; Huang, K. K., and Yang, C. S.: Liver Extract, Liver Ash and Iron in the Treatment of Anemia, J. Clin. Investigation **9**:533, 1930.

7. Elvehjem, C. A.: The Relative Value of Inorganic and Organic Iron in Hemoglobin Formation, J. A. M. A. **98**:1047 (March 26) 1932.

8. Reimann, F., and Fritsch, F.: Vergleichende Untersuchungen zur therapeutischen Wirksamkeit der Eisenverbindungen bei den sekundären Anämien, Ztschr. f. klin. Med. **115**:13, 1930.

Standards' pipettes and counting chambers. For the determination of the reticulocytes, smears of capillary blood were stained supravitally with brilliant cresyl blue, dried, counterstained with Wright's stain and mounted permanently after the methods of Hawes[9] and Cunningham.[10]

Iron was administered by mouth in the form of iron and ammonium citrate (brown scales) or pills of ferrous carbonate, U. S. P., and in a few instances other preparations of inorganic iron were used. Metallic iron in iron and ammonium citrate is about 17 per cent; that is, in each gram of the salt there is about 170 of metallic iron. In each pill of ferrous carbonate there is approximately 30 mg. of metallic iron. These values were used in estimating the dosage and its effects in individual cases.

CLINICAL MATERIAL

Eighty-four patients with hypochromic anemia, who responded well to iron, are under consideration here (table 1). They have been chosen

TABLE 1.—*Classification of Eighty-Four Cases of Hypochromic Anemia Responding to Iron*

Chief Etiologic Factors	Number of Cases	Percentage
Idiopathic hypochromic anemia with achlorhydria or hypochlorhydria	33	39
Chronic blood loss	35	42
Inadequate diet	10	12
Recent pregnancy and inadequate diet	2	7
Carcinoma of stomach and chronic blood loss	2	
Hodgkin's disease and chronic blood loss	1	
Amebic dysentery and chronic blood loss	1	
Total	84	100

from a large group of patients with different forms of anemia who have been carefully studied in this clinic during the past four years. Selection of the cases for the present study has been based arbitrarily on either at least a 1 per cent rise of hemoglobin per day and satisfactory clinical improvement following iron, or the absence of a type of anemia that cannot respond to iron and that has severe complications which experience has shown might hinder the effect of iron. Many of the cases had multiple etiology, for example, poor diet associated with a chronic loss of blood from peptic ulcer, or idiopathic hypochromic anemia with achlorhydria with chronic menorrhagia. No hypochromic pregnancy anemias which respond to iron are included, although there are a few cases of anemia in women in whom a previously terminated pregnancy had undoubtedly contributed to the anemia. There are also included two cases of cancer of the stomach with achlorhydria, one of Hodg-

9. Hawes, J. B.: A Study of the Reticulated Red Blood Corpuscles by Means of Vital Staining Methods: Its Relation to Polychromatophilia and Stippling, Boston M. & S. J. **161**:493, 1909.

10. Cunningham, T. D.: A Method for Permanent Staining of Reticulated Red Cells, Arch. Int. Med. **26**:405 (Oct.) 1920.

kin's disease and one of amebic dysentery, in all of which there had been a pronounced chronic loss of blood.

In the selection of suitable cases, it is important to exclude cases of anemia due primarily to severe infections, cancer, nephritis and certain other causes, because such complications hinder the action of iron in hypochromic anemia just as they hinder the effect of potent material in pernicious anemia.[11] Many of the eighty-four patients had such complications to a minor degree, but as a rule not sufficiently to hinder greatly the action of the iron medication.

Table 2 gives an additional list of forty-two cases of anemia of various etiologies in which large amounts of iron had been given and no response or a small response obtained. The majority of the patients had color indexes of 1 or more. Slight responses to iron were obtained

TABLE 2.—*Classification of Forty-Two Cases of Anemia in Which Adequate Trial with Iron Gave no Response or Only a Small Response*

Chief Etiologic Factors	Number of Cases
Cancer (stomach, large bowel, pancreas, metastatic)	6
Sepsis (pyelitis, cystitis, pneumonia, tuberculosis, abscess)	9
Chronic nephritis	4
Megalocytic anemia of unknown origin (including aplastic anemia)	8
Myelogenous luekemia	5
Scurvy	4
Hemolytic jaundice	3
Myxedema	1
Cirrhosis of the liver	2
Total number of cases	42

in only a few of the forty-two cases, and the color indexes were below 1. The patients with megalocytic anemia of unknown origin, leukemia, scurvy and hemolytic jaundice had color indexes above 1 and gave absolutely no response to iron. In addition to these cases, eight normal persons showed no response while taking between 0.3 and 2 Gm. of iron daily in the form of ferrous carbonate or iron and ammonium citrate. Mention should also be made of a group of patients with pernicious anemia in whom, during the response of the blood to liver extract or some other potent material, hypochromic anemia developed; they then responded to iron.

FACTORS NECESSARY IN ACCURATE CLINICAL INVESTIGATION OF THE EFFECTS OF IRON THERAPY

Early experiments of Whipple on the acute loss of blood in dogs seemed to lead to the conclusion that iron was of no value in the treat-

11. Minot, G. R., and Castle, W. B.: The Adequate Treatment of Anemia, Ann. Int. Med. **5**:159, 1931.

ment of anemia. The experiments of Williamson and Ets [12] seemed to lead to the same conclusion. Whipple's subsequent experiments showed that iron could be of considerable value in long-standing severe anemia, in which by prolonged severe bleeding and diet control the stores of hemoglobin-building material were reduced until regeneration was much slowed down. This process, which requires so long and is so difficult to produce in the dog, can take place frequently and apparently rather easily in man. This possibility was not recognized formerly, and because iron seemed to fail in so many kinds of anemia, it was thought by many to be useless in all kinds.

Ten years ago, Meulengracht [13] reviewed the difficulties of judging the effectiveness of iron in different kinds of anemia and the necessity of adequate control periods. At that time he was not aware of the value

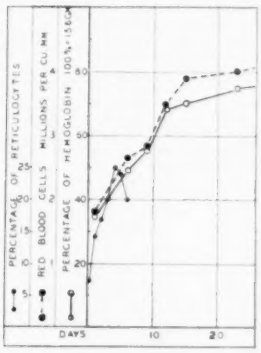

Chart 1.—The blood changes in a man with acute hematemesis from peptic ulcer, apparently having adequate stores of blood-building material. The response of the reticulocytes, red blood cells and hemoglobin to the acute blood loss was good, without the administration of iron, except after the fifteenth day.

of the reticulocyte reaction, but now, since the value of determining the effectiveness of iron by this prompt reaction has been shown, a portion of the difficulties has been overcome. In the clinical investigation of iron therapy in hypochromic anemia there are two factors of primary importance: first, the selection of suitable cases, and second, the establishment of adequate control periods.

Charts 1, 2 and 3, which are illustrative of these facts, represent the blood findings in three men, each of whom entered the hospital with loss of blood from peptic ulcer. Chart 1 represents the blood findings in a

12. Williamson, C. S., and Ets, H. N.: The Value of Iron in Anemia, Arch. Int. Med. **36**:333 (Sept.) 1925.

13. Meulengracht, E.: Large Doses of Iron in the Different Kinds of Anaemia in a Medical Department, Acta med. Scandinav. **58**:594, 1923.

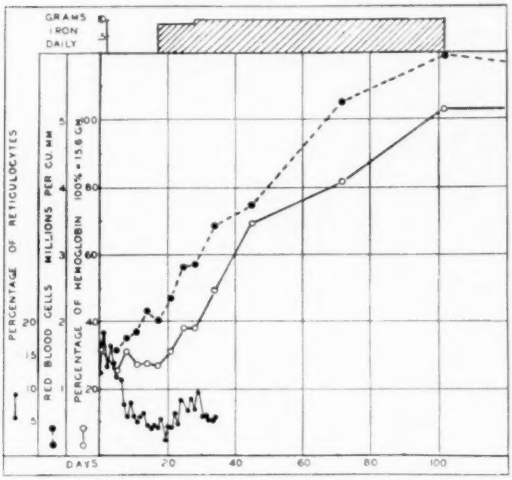
GRAMS IRON DAILY
PERCENTAGE OF RETICULOCYTES
RED BLOOD CELLS MILLIONS PER CU MM
PERCENTAGE OF HEMOGLOBIN 100% = 13.6 GM
DAYS

Chart 2.—The blood changes in a man with acute hematemesis from peptic ulcer, apparently having inadequate stores of blood-building material. There was a response of the reticulocytes and red blood cells, but the hemoglobin did not rise until after iron was administered. Note the development of a color index below 1.

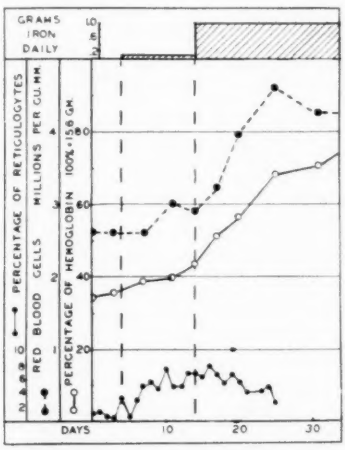
GRAMS IRON DAILY
PERCENTAGE OF RETICULOCYTES
RED BLOOD CELLS MILLIONS PER CU MM
PERCENTAGE OF HEMOGLOBIN 100% = 13.6 GM
DAYS

Chart 3.—The blood changes in a man with previous chronic blood loss from peptic ulcer. The stores of blood-building material had apparently been reduced, and the color index was below 1. A response of reticulocytes, hemoglobin and red blood cells occurred following the administration of 0.1 Gm. of iron. Note the more rapid response of the hemoglobin and red blood cells after the administration of 1 Gm. of metallic iron daily.

man who had acute hematemesis and showed marked anemia when he entered the hospital. The color index was 1; there was a pronounced response of reticulocytes to the loss of blood and a prompt rise of both hemoglobin and red blood cells. He required no iron to produce this response, and iron probably would have caused his blood to rise no faster. He apparently had a good hemoglobin-building reserve to meet the emergency. As recovery took place the color index began to decrease, and it is possible that iron at this later time would have hastened the return of the hemoglobin to normal. Chart 2 represents a similar situation, but an inability to meet the emergency, so that in spite of a high reticulocyte rise due to a loss of blood there were only a slow rise of red blood cells, no rise of hemoglobin and a lowering of the color index. The hemoglobin-building reserve was apparently low, and the administration of iron was of benefit, as shown by the reticulocyte response and the abrupt rise of hemoglobin and red blood cells and the rising color index. Chart 3 shows the blood findings of a man who had a history of a chronic loss of blood from duodenal ulcer. The color index was low, and there was very little evidence of any regenerative ability on the part of the bone marrow. A daily dose of 100 mg. of iron was somewhat effective, but a daily dose of 1 Gm. of iron produced a further reticulocyte response and caused the hemoglobin to rise faster. It must be emphasized that patients were on diets composed almost entirely of milk and cream. These patients were, therefore, from a hematologic point of view, somewhat similar to Whipple's dogs at various stages of bleeding.

The necessity for adequate control periods is well brought out by these cases. It is clear that anemia due to an acute loss of blood is unsuitable for the demonstration of the effectiveness of iron therapy. On the other hand, an acute loss of blood coming after a prolonged period of chronic loss of blood, poor diet or some other condition favoring anemia, such as achlorhydria, may provide an excellent opportunity for testing the blood-building power of iron preparations. In other words, to demonstrate the potency of a preparation of iron in a patient with hypochromic anemia, there must be a sufficient reduction in the patient's reserve of hemoglobin-building material to render him unable to manufacture more than a maintenance amount of hemoglobin.

There are various mechanisms that may produce such a deficiency if one takes into consideration the different types of hypochromic anemia which are known to respond to iron. These may be divided into four main classes: (1) chronic loss of blood; (2) dietary deficiency; (3) gastro-intestinal disorders, and (4) pregnancy. It is obvious that the store of hemoglobin-building material may be reduced by a loss of blood. A diet restricted especially in green vegetables, fruit and meat affords an insufficient supply of such material. Gastro-intestinal dis-

orders may interfere with the proper assimilation of this material in the food, as, for example, in the anemia associated with chronic dysentery.[14] This is also well exemplified by the type of anemia known as idiopathic hypochromic anemia with achlorhydria in which the absence of hydrochloric acid in the stomach is associated with an apparent inability to utilize hemoglobin-building substance in the food.[6a] In pregnancy the transfer of hemoglobin-building material from the mother to the fetus explains in part, at least, the frequent production of an iron-responding anemia in the mother, while a change in the secretory ability of the stomach of the mother during pregnancy probably also plays a part.[15] The rôle played by altered gastric function in the production of hypochromic anemia is of such great importance that it must be evaluated in any case even if some other cause for anemia is present.

THE DETERMINATION OF OPTIMAL IRON DOSAGE

Of course, iron dosage has been optimal if the blood response is rapid and if the patient makes satisfactory clinical improvement, but to reach a more definite conception of the appropriate dose certain objective facts are needed. Two kinds of tests have been used in order to approach this conclusion: the first is an arbitrary test; the second, a comparative test. For the arbitrary test the response of the reticulocytes and the rate of hemoglobin rise after iron were compared to certain standards and expressed in terms of percentage of those standards. For the comparative test the response of the reticulocytes and the hemoglobin after a small daily dose of iron for from eight to twelve days was compared to the response after a larger daily dose for a similar period of time. The arbitrary test as employed in the eighty-four cases responding well to iron will be discussed first.

The Arbitrary Test.—The standard for the response of the reticulocytes to iron has been taken from data given by Minot and Heath[16] and is shown in chart 4. Since the height of the reticulocyte rise after iron in hypochromic anemia is inversely proportional to the level of the red blood cells and hemoglobin, considered together, before treatment, the expected height of the reticulocyte rise may be determined for each case by referring to chart 4. This may be done best by averaging the

14. Keefer, C. S.; Yang, C. S., and Huang, K. K.: Anemia Associated with Chronic Dysentery, Arch. Int. Med. **47**:436 (March) 1931.

15. Strauss, M. B., and Castle, W. B.: The Aetiology and Treatment of Anaemia in Pregnancy, Lancet **1**:1198, 1932. Strauss, M. B.: Observations on the Etiology and Treatment of Anemia in Pregnancy, J. Clin. Investigation **11**: 809, 1932.

16. Minot, G. R., and Heath, C. W.: The Response of the Reticulocytes to Iron, Am. J. M. Sc. **183**:110, 1932.

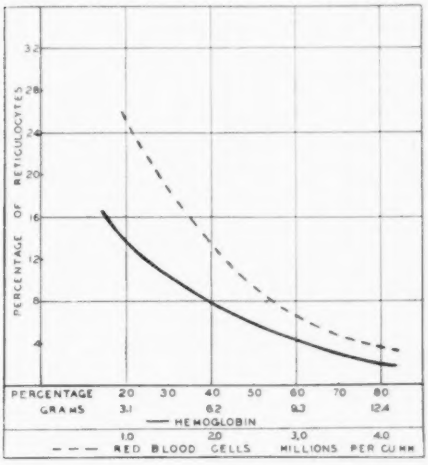

Chart 4.—The average response of the reticulocytes at the peak of their rise in cases of hypochromic anemia responding to iron. The red blood cell and hemoglobin levels, before treatment with iron was started, are recorded as abscissae. Taken from data given by Minot and Heath (Am. J. M. Sc. **183**: 110, 1932).

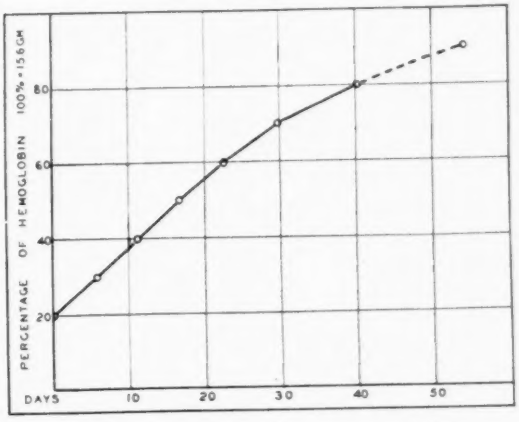

Chart 5.—The average rate of hemoglobin increase in eighty cases of hypochromic anemia during the administration of iron.

percentage of the expected maximal reticulocyte rise at the initial red blood cell level and at the initial hemoglobin level.

The standard for determining the expected rate of hemoglobin rise is shown in chart 5. This figure has been constructed as follows: Based on experience with more than two hundred cases, a rise of 1 per cent (0.16 Gm.) of hemoglobin per day may be assumed to be the lower limit of a satisfactory rate when the initial hemoglobin is below 50 per cent (7.8 Gm.). The number of days required for the hemoglobin to rise each 10 per cent when the rate was 1 per cent a day or faster was determined for each of eighty cases, according to the method described by Josephs.[17] The average was charted and is shown in chart 5. Rises in hemoglobin above 80 per cent occurred only in those patients who continued to improve steadily, whether or not the rate was 1 per cent per day. Therefore, the rate of hemoglobin rise above 80 per cent as expressed in chart 5 is optimal. It was the exception rather than the rule for the hemoglobin in an individual case to continue to rise throughout the entire course of improvement as evenly as the average which is shown in chart 5. In many cases there was considerable irregularity in the rate of hemoglobin increase. The curve for the average, however, compares well with that given by Josephs[17] for anemia in children responding to iron. When the hemoglobin is below 50 per cent, the rate is somewhat slower than that given by Josephs. Above this level it is faster and apparently corresponds more closely to his figures for the hemoglobin rise in children who received copper in addition to iron. This seems to contribute to the evidence that will be mentioned later that copper given in addition to iron in hypochromic anemia in adults does not have any definite influence.

The rate of hemoglobin rise in any given case during the administration of iron may be expressed in percentage of the expected rise as determined from chart 5. Thirty-four per cent of the eighty-four patients had hemoglobin rises due to iron therapy, which were satisfactory when judged by this method. Forty-six per cent had satisfactory reticulocyte rises when judged by the arbitrary test for the height of the reticulocyte rise after iron. The two tests are therefore fairly comparable, and they also afford a standard which requires of a case of hypochromic anemia rapid blood regeneration and therefore adequate iron dosage.

In judging the dosage of iron by this method, the average of the percentages of the expected reticulocyte rise and the expected hemoglobin rise was taken as the criterion. If the average was 100 per cent or over, the dosage arbitrarily was considered optimal; if below 100 per cent, the dosage was considered suboptimal.

17. Josephs, H.: Treatment of Anaemia of Infancy with Iron and Copper, Bull. Johns Hopkins Hosp. **49**:246, 1931.

In only about one half of the cases was there good correlation between the percentage of expected reticulocyte rise and the percentage of expected hemoglobin rise. The discrepancy shown by the remainder of the cases is probably due as much to the errors of the method as it is to the difference in the types of cases and variation in iron dosage. Occasionally in two similar cases there might be, in one, a low reticulocyte response and a high hemoglobin response, and in the other, a low hemoglobin response and a high reticulocyte response. Cases in which the etiology of the anemia was different showed similar discrepancies. The explanation for this state of affairs has not been discovered, but it may be dependent on different reserve powers for the manufacture of cells and for the formation of hemoglobin or on some fundamentally different cellular state of the bone marrow.

After determining in this manner what doses of iron had been optimal, it was apparent at once that the optimal dose varied a great

TABLE 3.—*Analysis of the Response to Iron in Thirty-Eight Cases of Hypochromic Anemia in which Patients Were Given 1 Gm. of Metallic Iron as Iron and Ammonium Citrate Daily*

	Total Number of Cases	Number of Cases Having Complications	Number of Cases Having Reduced or Absent Free Hydrochloric Acid in the Stomach After Histamine
Response over 100 per cent of the standard.....	16	2	5
Response less than 100 per cent of the standard..	22	8	11

deal from patient to patient. Thirty-four patients, as determined by the methods indicated, received an optimal dosage of iron, averaging 0.72 Gm. daily. Fifty patients received a suboptimal dosage, averaging 0.69 Gm. daily. However, there was a general trend for the smaller doses to produce submaximal responses. For example, in 40 per cent of twenty-one cases in which a dose of from 0.35 to 1 Gm. of metallic iron had been given daily, this dose was optimal; on the other hand, in only 19 per cent of twenty-six cases in which the dose was from 0.1 to 0.35 Gm. daily was this quantity optimal.

When a dose of about 1 Gm. of iron had been given and the response was submaximal in an individual case, there was often some complication, such as moderate sepsis with fever, that explained the unsatisfactory response. Many of the patients had idiopathic hypochromic anemia, a condition in which the absence of free hydrochloric acid in the stomach may interfere with the proper assimilation of iron.[6a] This is well exemplified in the analysis of the responses of thirty-eight patients to whom iron and ammonium citrate, containing 1 Gm. of metallic iron, was given daily (table 3). Of these patients, sixteen, or 42 per cent, had responses over 100 per cent of the standard, which would indicate

that the dosage had been optimal, and of these sixteen patients, five had idiopathic hypochromic anemia, and two additional patients had complications. Twenty-two of the thirty-eight patients, or 58 per cent, had responses less than 100 per cent of the standard, indicating a suboptimal dosage, and of these, eleven patients had idiopathic hypochromic anemia, and eight additional patients had complications. The same results appear when groups of patients receiving a smaller dosage of iron and ammonium citrate and those receiving ferrous carbonate are analyzed in this manner.

In comparing the cases of nine patients who received pills of ferrous carbonate with those of sixty-nine patients who received iron and ammonium citrate, the data showed that a smaller average dose of iron in the form of ferrous carbonate gave greater responses than the larger average dose of iron in the form of iron and ammonium citrate. It is not believed that there is as much discrepancy in the effect of these two iron preparations as this statement would seem to indicate. Evidence will be given subsequently regarding this point.

A considerable difference could be demonstrated when the average response of the thirty-three patients with idiopathic hypochromic anemia was compared to that of the forty-one patients with a chronic loss of blood. The average daily dose of iron was about the same in the two groups of cases, namely, 0.7 Gm. of metallic iron. The average percentage response of the arbitrary standard was maximal in only 29 per cent of the thirty-three cases of idiopathic hypochromic anemia, whereas it was maximal in 53 per cent of the forty-one cases of chronic blood loss.

A detectable response of reticulocytes and hemoglobin was generally noted with small doses of iron (less than 0.1 Gm. of metallic iron daily). One patient, who had chronic blood loss from the uterus, was remarkable in that her blood responded maximally to only 85 mg. of metallic iron in the form of iron and ammonium citrate daily. On the other hand, the following dosages were demonstrated in three patients to be absolutely ineffective: 85, 50 and 60 mg. of metallic iron daily.

It would appear, therefore, that a dose of iron that is optimal for one case of hypochromic anemia may be suboptimal for another, but, in general, small doses of iron are likely to be suboptimal. When a large dose of iron (1 Gm. of metallic iron daily) is given and the response is submaximal there may be some complication. An optimal dose of iron in hypochromic anemia due to an uncomplicated chronic blood loss and without achlorhydria is probably a suboptimal dose in idiopathic hypochromic anemia with achlorhydria. These points are brought out perhaps more strongly in the study of individual cases, and will be further illustrated by the comparative test of iron dosage.

The Comparative Test.—The comparative test is that which has been employed by various investigators in the comparison of the effect of several substances on the formation of blood. The test consists in the uniform daily administration of a substance (in this case a certain dose of iron), followed immediately by the uniform daily administration of a second substance (or a larger dose of iron). In this way any additional reticulocyte response and any faster rate of hemoglobin rise occurring during the administration of a larger dose of iron are quite conclusive of a more effective iron dosage. If no reticulocyte rise is obtained and the anemia is sufficient to permit one when a larger dose of iron is given, and if a response occurred when the first dose was given, the first dose of iron is presumably optimal. A similar state of

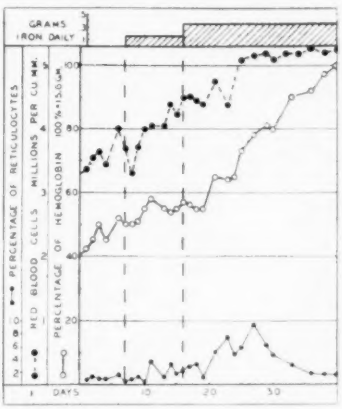

Chart 6.—The blood changes in a case of hypochromic anemia following the daily administration of first 180 mg. of metallic iron as iron and ammonium citrate and subsequently 360 mg. The latter dose was far more effective, as shown by the greater reticulocyte response and the increased rate of hemoglobin formation.

affairs holds for the rate of increase of hemoglobin, but one must judge the rate according to the initial hemoglobin level, for it often is faster at low hemoglobin levels than at high levels. This comparative test is similar to the method used by Reimann and Fritsch [8] for the demonstration of the superiority of ferrous salts over ferric salts, with the exception that the change between two doses is made abruptly without a period of rest between the doses. The test is illustrated in chart 6, in which 180 mg. of metallic iron, as iron and ammonium citrate daily, produced a slight reticulocyte response and a hemoglobin rise, but 360 mg. was far more effective. The response to the second dose was well over the maximal response, when judged by the arbitrary test, so that in this particular case there is good reason for thinking that 360 mg.

of iron daily was optimal. Table 4 gives the results in all of the cases tested in this manner. It is seen from this table that doses as high as 0.76 Gm. of iron daily were suboptimal, whereas in several other cases smaller doses of iron than this were apparently optimal.

Data from a case of idiopathic hypochromic anemia are shown in chart 7, which illustrates by such a comparative test the fact that the same dose of an iron salt may be more effective if prepared in a particularly suitable form for assimilation. As is well known, pills of ferrous carbonate may be made too firm and with time may become

TABLE 4.—*Comparative Responses of Hypochromic Anemia to Different Doses of Iron (Ferric and Ammonium Citrate Unless Otherwise Indicated)*

Etiologic Factors	Initial Dose, Gm. of Iron	Dose Which Gave Second Reticulocyte Response, Gm. of Iron	Dose Which Gave Faster Hemoglobin Rise, Gm. of Iron	Dose Which Did Not Give Faster Hemoglobin Rise, Gm. of Iron
Idiopathic hypochromic anemia; chronic blood loss	0.085	0.19	0.34	0.19
Restricted diet	0.09	0.18	0.18	....
Chronic blood loss	0.18	0.36	0.36	....
Idiopathic hypochromic anemia	0.19	0.85	0.51	....
Idiopathic hypochromic anemia	0.17	1.00	1.00	....
Chronic and acute blood loss	0.085	1.00	1.00	....
Idiopathic hypochromic anemia; chronic blood loss	0.22	....	1.02	....
Chronic and acute blood loss	0.34	1.02	1.02	....
Idiopathic hypochromic anemia	0.17	1.00	1.00	....
Idiopathic hypochromic anemia	0.21	1.00	....	1.00
Chronic blood loss	0.34	....	....	1.00
Idiopathic hypochromic anemia; chronic arthritis	0.085	....	....	1.00
Idiopathic hypochromic anemia	0.25	....	....	0.34
Chronic blood loss	0.76	....	....	1.00
Restricted diet	0.09*	....	0.35*	....
Chronic blood loss	0.46*	....	0.96	....
Ameblc dysentery	0.35*	....	0.52*	....
Restricted diet	0.06*	....	....	0.35*
Postpregnancy, acute blood loss	0.85†	....	....	2.60†

* Ferrous carbonate.
† Ferrum reductum.

hard and resistant. If the preparation is powdered and administered in gelatin capsules, it is in a form more readily available for solution in the gastro-intestinal tract. As is shown in chart 7, the patient received the equivalent of 4 pills of ferrous carbonate (120 mg. of metallic iron) a day for ten days, to which she responded only slightly. When she was given the same number of pills after they had been powdered, a definite second reticulocyte response and a marked rise in the hemoglobin and red blood cells occurred. The equivalent amount of metallic iron given in the form of ferric sulphate and sodium bicarbonate caused no noticeable increased effect, whereas the equivalent amount of iron in the form of ferrous sulphate and sodium bicarbonate again produced a definite reticulocyte response. These two combinations of substances were given

with the intention of showing that the reduced form of pills of ferrous carbonate is more effective than the oxidized form (ferric carbonate). The latter form presumably is present to a large extent in pills that have been prepared a long time previous to use. A final moderate reticulocyte response occurred when iron and ammonium citrate in a larger daily dose (1 Gm. of metallic iron) was given. This figure, then, shows how different preparations containing the same dose of iron may vary in their effectiveness and how a larger dose of iron may be more effective than a smaller dose.

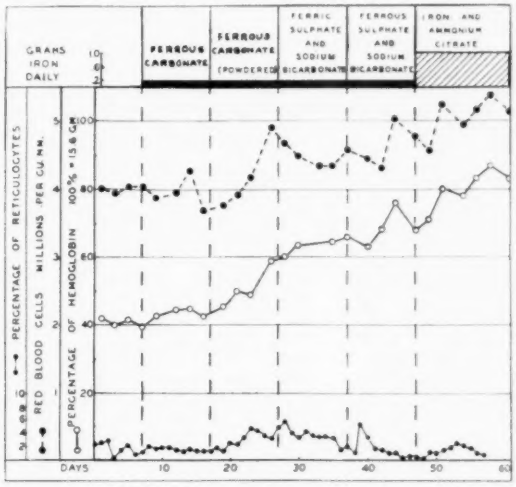

Chart 7.—The blood changes in a case of hypochromic anemia during the administration of iron in different physical and chemical states. Note the lack of response to pills of ferrous carbonate given as such, and the excellent response to the same preparation given in powdered form. None of these preparations in a dose of 0.2 Gm. of metallic iron was more effective than 1 Gm. of metallic iron given daily in the form of iron and ammonium citrate.

THE UTILIZATION OF IRON ADMINISTERED ORALLY

It is well known that most of the iron administered orally leaves the body in the feces. To what extent the iron is absorbed or is reexcreted into the intestine is not known. However, the amount of iron contained in the newly formed hemoglobin may serve as an index of the iron retained by the body. This idea was adopted to arrive at a definite conclusion regarding the amount of iron that may have been absorbed and utilized in the building of hemoglobin in the cases studied. The percentage of utilization of iron was determined for each case. For this it is necessary to know the blood volume, which, for the present purpose,

was assumed to be 5 liters for each subject. The grams of hemoglobin per hundred cubic centimeters of blood gained during the period of hemoglobin rise is therefore multiplied by 0.003, a convenient, average figure for the amount of iron in hemoglobin.[18] The final product represents the total amount of iron gained in the circulating blood during the period of hemoglobin rise. The percentage of iron utilization is then determined by dividing the total amount of iron gained in the circulating hemoglobin ($\times$ 100) by the amount of iron given orally.

Chart 8 records the percentage of utilization of iron in eighty-one cases. The percentage of utilization of small doses was, of course, much higher than that of large doses. Seven patients who received a total of less than 5 Gm. of metallic iron during the entire period of treatment

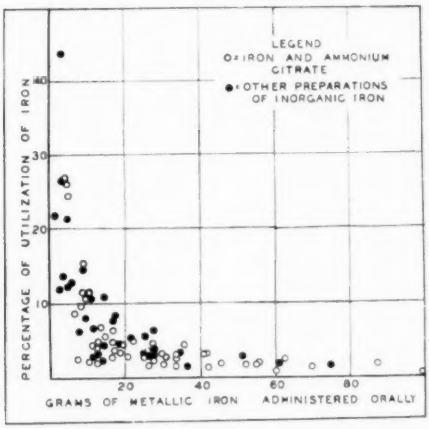

Chart 8.—The percentage of utilization of iron in the formation of new circulating hemoglobin in eighty-one cases of hypochromic anemia during the entire period of hemoglobin rise. The percentage of utilization of iron from iron and ammonium citrate is shown to be similar to that of iron from other preparations.

attained a utilization of over 20 per cent. The few cases in which there were low dosage and low utilization were, for the most part, cases that were complicated by factors known to inhibit the formation of blood, such as sepsis or a malignant process. The figure shows, also, that the percentage of utilization of iron from iron and ammonium citrate was similar to that from the other forms of iron given.

Additional data have shown that the percentage of utilization of iron early in the course of recovery from anemia tends to be considerably higher than the figures recorded in chart 8, which are for the total period

18. Murphy, W. P.; Lynch, R., and Howard, I. M.: The Value of Determinations of the Iron Content of Whole Blood, Arch. Int. Med. **47**:883 (June) 1931.

of recovery. Three cases showed, early in the period of recovery, a percentage of utilization of about 50. That iron may be utilized to such a large extent is a fact that is not ordinarily appreciated. The average utilization in all cases during the entire period of recovery was 3.4 per cent. In contrast to this, the utilization in fifty-eight uncomplicated cases, during the first thirty days after iron therapy was commenced, was 11.8 per cent. The average utilization of iron in the thirty-three cases of idiopathic hypochromic anemia during the total period of recovery was 3.1 per cent, and a further contrast is shown by the fact that in the forty-one cases of anemia without achlorhydria due to a chronic blood loss the utilization was 5.5 per cent. It is to be expected that the percentage of utilization of iron in idiopathic hypochromic anemia should be less than that in anemia due to a chronic blood loss without achlorhydria, since the absence of free hydrochloric acid in the gastric contents probably is a factor in preventing adequate absorption of iron.

The information obtained by the determination of the percentage of utilization of iron must not confuse the fact already illustrated by the arbitrary and comparative tests, that larger doses of iron are definitely more valuable than smaller doses. That large doses of iron are utilized to a lesser degree than small doses simply means that the amount of hemoglobin rise, though large, is not proportionately as great as the size of the dose of iron.

A comparison of the parenteral administration of iron with the oral administration of iron as regards the utilization in the building of hemoglobin is interesting, and is discussed in a separate communication.[19] Factors of intestinal absorption do not enter into the problem of the utilization of iron administered parenterally. In cases of hypochromic anemia in which the patients are given iron by the parenteral route, the percentage of utilization approaches 100, and therefore the amount of iron injected is closely related to the amount of iron gained in the circulating hemoglobin.

THE MAINTENANCE DOSE OF IRON IN IDIOPATHIC HYPOCHROMIC ANEMIA

Patients with idiopathic hypochromic anemia, in contrast to those with hypochromic anemia due to a chronic blood loss or other causes, usually require either the continuous administration of iron or frequent courses of iron therapy in order to maintain a normal level of hemoglobin.[20] There have been nineteen patients with this disease who have

19. Heath, C. W.; Strauss, M. B., and Castle, W. B.: Quantitative Aspects of Iron Deficiency in Hypochromic Anemia: The Parenteral Administration of Iron, J. Clin. Investigation **11**:1293 (Nov.) 1932.

20. Heath, C. W.: Idiopathic Hypochromic Anemia with Achlorhydria, M. Clin. North America **15**:1015, 1932. Witts.[2]

been followed for over one year and who omitted iron following the initial recovery of their blood to normal. In all but five patients a definite drop in the hemoglobin occurred, which soon returned to normal when adequate iron medication was reinstituted. Of the five patients who maintained their hemoglobin level after iron was omitted, two showed a return of the acidity of the gastric contents to normal. One of these was a man who for years previous to treatment with iron had indulged excessively in alcohol but did not do so after treatment was commenced. In these two cases, an improvement in gastric function undoubtedly permitted a more normal absorption of hemoglobin-building substances of the food, and therefore rendered the renewal of iron medi-

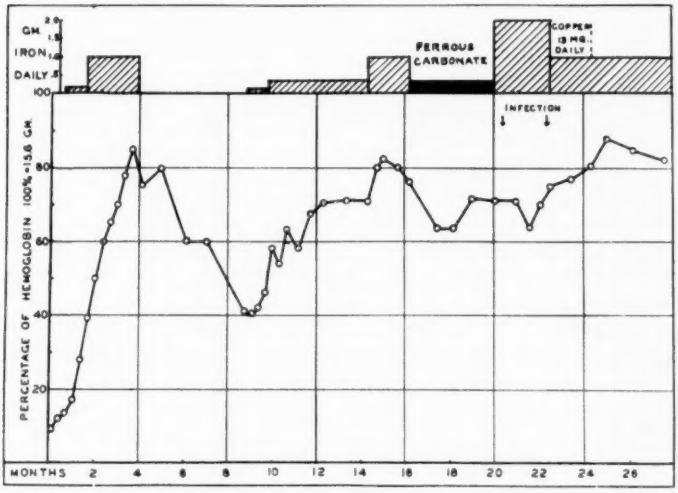

Chart 9.—The changes in the hemoglobin percentage in a case of idiopathic hypochromic anemia observed over two years. Iron was administered in the form of iron and ammonium citrate except as indicated. Note (1) the prompt decrease of hemoglobin when iron was omitted, (2) the rise of hemoglobin over 80 per cent only when 1 Gm. of iron daily in the form of iron and ammonium citrate was given and (3) the failure of 2 Gm. of iron daily to increase the hemoglobin in the face of infection.

cation unnecessary. The remaining three patients, who to date have not required a renewal of iron medication, probably will eventually need it, if the complete achlorhydria persists.

Chart 9 represents a prolonged observation on a patient with idiopathic hypochromic anemia who has required iron to maintain the hemoglobin level. The hemoglobin fell gradually over the course of four months when iron was omitted. In addition, the chart demon-

strates a number of interesting points regarding iron therapy. When iron therapy was renewed in this patient, 80 mg. of iron as iron and ammonium citrate daily produced an unsatisfactory rise of hemoglobin (only 10 per cent in one month). Three hundred and seventy-five milligrams apparently produced a somewhat faster response of hemoglobin, but not as rapid as when the patient was first treated and received iron in the large dose of 1 Gm. a day. The hemoglobin fell again when 350 mg. of iron was given in the form of ferrous carbonate. Then the occurrence of an upper respiratory infection with fever lasting for nearly two months apparently prevented the hemoglobin from rising over about 70 per cent, in spite of a daily dose of 2 Gm. of iron. Thirteen milligrams of metallic copper was then given in addition to iron, but it cannot be said that it accomplished more than if iron had been given alone. The hemoglobin rose from 80 to 90 per cent when iron was given without copper.

It is difficult to say what would be the correct minimum maintenance dose of iron for this patient. A daily dose of 375 mg. of iron maintained the hemoglobin at 70 per cent, and it is likely from experience with other cases that if this dosage had been given from the time of the first recovery period it would have kept the patient in a good state of health. This is similar to the maintenance dose suggested by Witts,[2] which he states is not more than one third of the minimum effective curative dose, or about from 0.3 to 0.5 Gm. of iron in the form of ferric and ammonium citrate, or from 0.07 to 0.1 Gm. in the form of ferrous carbonate. It is logical that a smaller dose of iron is needed for the replacement of the normal loss of iron by excretion than for the building up of large amounts of new hemoglobin and the body reserves. However, in one patient 0.12 Gm. of iron daily in the form of ferrous carbonate was insufficient to maintain the hemoglobin at a level of 80 per cent. Iron as iron and ammonium citrate in a daily dose of 0.5 Gm. was insufficient in another patient while she was suffering from a recurrent loss of blood, but when the loss of blood had ceased, a considerably smaller dose was apparently satisfactory.

There is no question but that patients with mild cases of idiopathic hypochromic anemia with achlorhydria will sustain their blood level while taking an adequate diet, but when an additional cause for anemia occurs, such as a chronic or an acute loss of blood, a considerable degree of anemia may be produced which would not occur in a normal person. This can be attributed to small reserves of hemoglobin-building substances in the patient with idiopathic hypochromic anemia, even at a time when the hemoglobin level is nearly normal. On the other hand, certain patients with idiopathic hypochromic anemia, even while taking a proper diet and one rich in iron-containing foods and protein and not suffering from a chronic blood loss or other causes of anemia,

cannot maintain their hemoglobin level for more than several weeks without taking relatively large doses of iron daily (from 0.3 to 1 Gm. of iron as iron and ammonium citrate).

The maintenance dose of iron thus seems to vary considerably in different patients and also in individual patients at different times. Much depends on the reserve of iron and possibly other hemoglobin-building substances in the body, on the extent of the gastro-intestinal defect and on the composition of the diet. It is therefore necessary in treating these patients to adjust the maintenance dose of iron to the needs of the given patient, frequent hemoglobin determinations being necessary. It is probable, if large doses of iron are persisted in for a long time after the hemoglobin reaches normal, that the iron stores in the body may be increased. This would allow the hemoglobin level to be maintained for a certain time without iron being administered by mouth. One or two courses of iron therapy a year, lasting several months each, designed to maintain the store of iron in the body, will then be sufficient in many cases to keep the hemoglobin at a normal level, but it seems wiser to administer the drug with regularity.

TOXIC SYMPTOMS FOLLOWING THE ORAL ADMINISTRATION OF IRON AND AMMONIUM CITRATE

Certain disagreeable symptoms are not infrequently met with when iron is administered orally to patients. They have been observed especially when iron and ammonium citrate is given, and the present discussion is concerned with symptoms observed following the administration of this drug, which has been employed to a large extent in this study. Low abdominal cramps and diarrhea are the most common complaints, but these are apt to occur only during the first few days of iron therapy. If the iron medication is persisted in, the diarrhea and cramps usually disappear. Ambulatory patients are much more apt to experience these symptoms than patients who are in bed. Constipation may sometimes accompany the giving of large doses. General malaise, nausea and vomiting, symptoms that follow the parenteral administration of iron and ammonium citrate,[19] have been observed in a few instances. However, these symptoms have never appeared extremely severe or dangerous.

The extremely toxic properties of iron become evident practically only when it is administered parenterally in doses above 16 mg. Some of the toxic symptoms resulting from iron administered orally are due perhaps to an unusually rapid absorption of iron. Hurst[21] has described an unusual case of acute iron poisoning in a patient who was given a large amount of iron orally. It seems wise, therefore, as a

21. Hurst, F. H.: A Case of Iron Encephalopathy, Guy's Hosp. Rep. **81**:243, 1931.

routine, to commence treatment with a small daily dose of iron (2 Gm. of iron and ammonium citrate), gradually increasing it in the course of a few days to the desired amount. Minor symptoms are to be disregarded, since these generally disappear in the course of time as the patient persists in the treatment.

The maximum amount of iron administered orally that is eventually tolerated by patients is, as a rule, very large. One gram of metallic iron, in the form of 6 Gm. of iron and ammonium citrate daily, was taken with ease by the majority of patients. Only three of the sixty-three patients with hypochromic anemia who received iron and ammonium citrate in this dosage had untoward symptoms. In one patient the dose of 0.5 Gm. of metallic iron could not be exceeded because of diarrhea and abdominal cramps. On the other hand, in one patient symptoms of intolerance did not develop until 2 Gm. of metallic iron, as iron and ammonium citrate, was given daily, and even this large dose was well tolerated by several other patients.

THE VALUE OF COPPER THERAPY IN HYPOCHROMIC ANEMIA

Because of the effectiveness of copper in addition to iron on nutritional anemia in rats [22] and on nutritional anemia in children,[17] there has recently been considerable speculation regarding the possible value of copper in hypochromic anemia in adults. The experimental data at hand suggests that the addition of copper adds no beneficial effect to that of iron in adult hypochromic anemia. As described, a curve representing the average maximal hemoglobin response of eighty patients with hypochromic anemia who were treated with large doses of iron has been constructed. Above the level of 50 per cent of hemoglobin, the rate of hemoglobin increase, as shown by this curve, is faster than that shown by a similar curve constructed by Josephs [17] for anemia in children treated by iron alone. This faster rate of hemoglobin rise seems to correspond more closely to Josephs' figures for the rate of hemoglobin increase in children who received copper in addition to iron. Chart 9, as has been explained, illustrates in a case of idiopathic hypochromic anemia the failure of the addition of copper to iron in bringing about a more complete restoration of the hemoglobin to normal than iron alone. Several similar experiments have likewise shown no conclusive evidence that copper added to iron is of value. This is not in accord with the work of Mills [23] and of Adamson and Smith,[24] who

22. Hart, E. B.; Steenbock, H.; Waddell, J., and Elvehjem, C. A.: Iron in Nutrition: VII. Copper as a Supplement to Iron for Hemoglobin Building in the Rat, J. Biol. Chem. **77**:797, 1928. Myers, V. C., and Beard, H. H.: Studies in the Nutritional Anemia of the Rat, J. Biol. Chem. **94**:89, 1931.

23. Mills, E. S.: Idiopathic Hypochromemia, Am. J. M. Sc. **182**:554, 1931.

24. Adamson, J. D., and Smith, F. H.: Chronic Chlorosis, Canad. M. A. J. **24**:793, 1931.

believe that iron and copper are more effective in the treatment of idiopathic hypochromic anemia than iron alone.

It is well known that small amounts of copper and other metals are present as impurities in pharmacopeial preparations of iron salts, and it has been thought that these impurities may have a share in the effectiveness of these preparations. However, a solution of iron and ammonium citrate, freed from the metals of the copper-arsenic group by hydrogen sulphide, produced an excellent response in one case of idiopathic hypochromic anemia.

It is felt that the influence that the addition of copper to iron may have in the treatment of hypochromic anemia in adults is at the most a minor one. Copper may perhaps hasten the recovery of patients with certain types of anemia. The same final results may be attained, however, by large doses of inorganic iron salts. This fact, together with the possible eventual toxic effect of copper, renders it inadvisable to give copper salts as a routine measure in cases of hypochromic anemia.

COMMENT

Evidence has been given showing that the optimal dose of iron administered orally to patients with hypochromic anemia varies considerably in different persons. Therefore, a single optimal dose for all patients cannot be defined. Frequent determinations of the hemoglobin are necessary in each individual case in order to determine whether or not the dose that is being given is adequate. The rule that the hemoglobin should rise at a faster rate than 1 per cent per day when the hemoglobin is below 70 per cent of normal may serve as a rough guide for judging the adequacy of a given quantity of iron.

If the hemoglobin response is much less than 1 per cent per day, doubt is cast on the adequacy of the iron dose, providing the anemia is of a kind that can be expected to respond well to iron, and providing no complications, such as sepsis or severe damage to organs, are present to inhibit the effectiveness of iron.

Sepsis, malignant processes, chronic nephritis, cirrhosis of the liver or other complications, which may themselves be etiologic in anemia, do not contraindicate the use of iron therapy. Hypochromic anemia due to a poor diet or a chronic loss of blood and responding to iron may accompany these conditions. For example, the anorexia accompanying typhoid fever or pulmonary tuberculosis may lead to the consumption of a diet low in many factors, including hemoglobin-building substances; the chronic loss of blood in cancer of the stomach or the hematemesis in cirrhosis of the liver may be the primary cause of hypochromic anemia in conditions responding to iron. The etiologic factors of the anemia in these conditions are usually difficult to judge, but may often be ascertained by an adequate trial with iron and by a complete study of the case.

To be certain of giving an adequate amount of iron in hypochromic anemia, it is necessary to give large doses, such as 6 Gm. of iron and ammonium citrate, corresponding to 1 Gm. of metallic iron daily. Economically, there is no objection to the administration of large amounts of inorganic iron, such as there is to the administration of large amounts of liver extract in the treatment of pernicious anemia, and as a rule large amounts of iron are well tolerated when given orally.

The problem of the oral administration of iron is one involving the quantitative correlation of the dosage with the influence on hematopoiesis. The clinical field for testing iron preparations may be quite well standardized by the careful selection of cases and the employment of adequate control periods. The effectiveness of iron preparations of unknown or doubtful value may then be compared to well known potent preparations. In this way accurate knowledge of the adequacy of treatment of human anemia with iron can be attained. Such knowledge will contribute to the better understanding and control of the etiologic factors in hypochromic anemia.

SUMMARY AND CONCLUSIONS

1. Eighty-four cases of hypochromic anemia have been analyzed with respect to the hematopoietic response to the oral administration of iron.

2. The factors necessary in the accurate clinical investigation of the effects of iron therapy are: (1) the careful selection of suitable cases with regard to their type and etiology and the absence of complications and (2) the establishment of adequate control periods.

3. An arbitrary test has been described whereby the hematopoietic response to iron may be judged quantitatively, and the adequacy of the dosage of iron determined.

4. A comparative test has been described whereby several preparations of iron may be compared with one another as to potency.

5. Optimal dosage of iron in hypochromic anemia, as judged by these tests, varies in different persons. Submaximal responses to large doses of iron are most often present in cases of idiopathic hypochromic anemia with achlorhydria and in cases complicated by sepsis, a malignant process or other conditions. Small doses of iron are, in general, less effective than large doses.

6. The percentage of utilization of orally administered iron, as determined by the total amount of iron gained in the circulating hemoglobin, varies inversely with the size of the dosage. It is possible, during the period of rapid gain of hemoglobin, when iron dosage orally is low, to have as much as 50 per cent of utilization. The average percentage of utilization of iron in the eighty-four cases during the

entire period of recovery was 3.4. The percentage utilization of iron in idiopathic hypochromic anemia is less than in uncomplicated hypochromic anemia due to a chronic loss of blood.

7. Patients with idiopathic hypochromic anemia usually require a continuation of iron therapy indefinitely. The maintenance dose of iron in these cases is usually smaller than the dose required for maximum blood regeneration in the period of recovery, but varies with individual cases.

8. Toxic symptoms following the oral administration of iron and ammonium citrate not infrequently occur, but the maximum amount of iron administered orally in this form that is eventually tolerated by the patients is, as a rule, large (from 1 to 2 Gm. daily).

9. It is felt that the influence that the addition of copper to iron may have in the treatment of hypochromic anemia in adults is at the most a minor one, and that it is inadvisable to give copper salts as a routine measure in hypochromic anemia in adults.

10. To be certain of giving adequate amounts of iron in hypochromic anemia, it is necessary to give large doses, such as 6 Gm. of iron and ammonium citrate daily, corresponding to 1 Gm. of metallic iron. Ferrous salts can be equally effective in somewhat smaller doses.

Book Reviews

Pituitary Body, Hypothalamus, and Parasympathetic Nervous System. By Harvey Cushing, Professor of Surgery (Emeritus), Harvard University, and recently Surgeon-in-Chief, Peter Bent Brigham Hospital, Boston. Price, $5. Pp. 234, illustrated, indexed. Springfield, Ill.: Charles C. Thomas, 1932.

This latest book of Dr. Cushing's has been available before in sections, for it comprises the papers that were the foundation for four lectures on related subjects: The Lister Memorial Lecture given before the Royal College of Surgeons of England on July 9, 1930; the William Henry Welch Lecture given at Mount Sinai Hospital, New York, on April 30, 1931; the Alpha Omega Alpha Lecture given at Yale University, on Feb. 24, 1932, and the Balfour Lecture given at the University of Toronto on Lister Day, April 8, 1931. Each paper presents an aspect, clinical or experimental, bearing on the function and interdependence of the pituitary body, hypothalamus and parasympathetic nervous system, and provides in itself ample fact for new clinical concept and for imaginative rumination.

Left separate, the papers may lose some force because only one facet of the question is touched on in each of them. Brought together, however, as has been done in this book, they add to each other, to round out a complete picture which stimulates the imagination in a way that is quite overwhelming. The book reads as easily as a novel, despite its colossal erudition, and presents a fascinating opportunity to those who enjoy following the reflections of a first-class and vastly experienced intelligence on a romantic and little understood subject.

The first paper, "Neurohypophysial Mechanisms from a Clinical Standpoint," surveys the evidence concerning the functions of the anterior hypophysis, infundibulum, posterior hypophysis and hypothalamus, and their dependence on each other. Clinical examples are described in which there have been lesions of one or the other of these structures, and the resultant symptoms, or lack of them, are correlated with the physiologic facts from which various current hypotheses have been evolved.

The second paper, "Posterior Pituitary Hormone and Parasympathetic Apparatus," is a remarkable experimental study of the effect of the introduction of different substances into the cerebral ventricle. It is divided into eight parts, the first of which describes the reaction of human subjects to intraventricular pituitary extract. The others go on to describe similarly the effects of intraventricular pilocarpine, histamine, atropine and tribromethanol, to show the counteractive effects of some of these substances, and to contrast their intraventricular effects with those produced when they are injected elsewhere in the body. To describe and discuss the many astonishing phenomena which were produced is not the function of this review. Suffice it to say that enough hitherto undiscovered information is accumulated about the action of these drugs when placed directly in the neighborhood of the neurohypophyseal mechanism to stimulate a great advance in knowledge of it, as well as to suggest new routes for investigative method.

The third paper is one that attracted attention everywhere, since it described for the first time, in a style unsurpassed for its clarity and vision, a new and heretofore unrecognized clinical syndrome, "Pituitary Basophilism." So keen was the discernment in ferreting out this rare and unusual pituitary aberration, and so accurate was the differentiation of its symptoms, that the underlying pathologic process, basophil adenoma of the hypophysis, was actually correctly predicted in cases which had previously been reported by other authors as showing polyglandular dystrophies of unknown origin.

The fourth paper, "Peptic Ulcer and the Interbrain," is perhaps more speculative than the others, and yet Dr. Cushing is always careful not to go from fact to fancy without forewarning the reader, and without giving him the groundwork

and leaving him the leeway to form his own conclusions. A number of cases are cited in which there has been disturbance in the neurohypophyseal mechanism, and in which peptic ulcer, acute or chronic, has been an associated finding. To these cases are added certain experimental facts tending to shed more light on the neurogenic theory of ulcer formation. That the incidence of peptic ulcer as a complicating factor in intracranial pathology is high is incontrovertible.

It is always a temptation for a reviewer to make his review a synopsis. While that could have been done in this instance, it was felt that to provide a mere recital of salient facts would have led some readers of these paragraphs to feel that the essentials could be absorbed from it without digesting the original. That is less true of this book than of any other of similar scope in this reviewer's ken. The manner in which the subject matter is presented, the fields that are opened to the reader's imagination and the way in which his knowledge is not only brought to date, but carried into the future make it imperative that the work itself be read. And more is the wonder when one considers that it is the work of a man who has always carried more than his share of active clinical burden sufficiently well as to be assured of a place in posterity as one of the great surgeons of all time.

Diseases of the Thyroid Gland. By Cecil A. Joll. Price, $20. Pp. 682. St. Louis: C. V. Mosby Company, 1932.

This book is presented as "an account of thyroid diseases in sufficient detail to be of value to senior students and practitioners of medicine, and even possibly to consultants who may be without special opportunities for the frequent observation of goitrous patients."

The opening chapters of the book, in which the structure, development and physiology of the thyroid gland are reviewed, are of especial interest and value in view of the recent advances in knowledge of these subjects. One chapter is devoted to the structure and physiology of the parathyroid glandules. This is followed by several chapters dealing with detailed clinical, pathologic and physiologic considerations of inflammatory and parasitic diseases of the thyroid gland, lymphadenoid goiter, developmental abnormalities, simple goiter, the hypothyroid states, neoplasms, thyrotoxicosis and the cardiovascular system in thyrotoxicosis. One chapter is devoted to a consideration of medical treatment and of treatment by irradiation for primary thyrotoxicosis. Surgical treatment of primary thyrotoxicosis is described in detail, and anesthesia, surgical technic in various types of cases and postoperative complications are all carefully considered and described.

Throughout the book illustrations are used profusely. There are many excellent colored plates. The illustrations are a distinct aid to avoidance of confusion in terminology. Carefully prepared lists of synonyms also help to avoid such confusion.

So many considerations of thyroid disease are hypothetic that it would seem impossible for any book on the subject to meet with the complete agreement of all readers. The author has given the principal opinions deserving of consideration on most of the controversial aspects of thyroid disease, and has also expressed his personal opinion in each case. Not all of the opinions so expressed coincide with the views most widely held in this country. This does not detract in the least from the value of the work, however, because ample consideration is given to the opposing views, and because the established fundamental principles of diagnosis and treatment are supported throughout the book.

The technic of surgical operations in various types of goiter is described in meticulous detail, and the recognition and treatment of postoperative complications are thoroughly considered.

The bibliography is most complete and is arranged at the ends of the chapters, thus greatly enhancing its value to those more than casually interested in the subject.

The book, beside being useful to the groups indicated in the author's preface, should prove of value to students of diseases of the thyroid gland and as a reference work.

Streptococci in Relation to Man in Health and Disease. By Anna W. Williams. Price, $5. Pp. 260. Baltimore: Williams & Wilkins Company, 1932.

The attempt to simplify for the student the vast complexity of modern medicine by the monographic method receives a notable addition in Dr. Williams' book on streptococci. For years a thorough student of bacteriologic problems and always on the firing line in the battle against disease, she assembles here a great storehouse of knowledge on all matters pertaining to this ubiquitous and treacherous group of micro-organisms. In matters dealing primarily with the biologic aspects of the problem, Dr. Williams writes with authority and confidence; her personal interpretations are both stimulating and convincing. But the sections dealing with clinical relations — applied bacteriology, if you will — lack, perhaps, a little of the spontaneity of the earlier chapters. The author has achieved the purpose, to be sure, of assembling all the important information, but here there is more the atmosphere of a compendium. The important questions (to the clinician) of focal infection and elective localization, for example, are dealt with in a slightly vacillating manner, and after the extensive summary of "streptococcic claims" in the etiology of rheumatic fever, one is disappointed that Dr. Williams is silent as to what she herself really thinks there is of sense, if any, in all this tangle. The summary (page 193) to the effect that "there is evidence to substantiate the hypotheses that hypersensitiveness or hyperergy to various strains of streptococci among alpha, gamma and beta types is the cause of an acute clinical rheumatic fever attack in those who by reason of several other factors also are ready for such an attack" is a *reductio ad absurdum*, which is hardly fair to the reader, when one might have said, "we really do not know at present just what the relation of streptococci to rheumatism is." One is also surprized to find that the rôle of streptococci in the common disease tonsillitis receives only casual mention, when a whole chapter is given to septic sore throat, a relatively insignificant subject. Even more disappointing is the lack of analysis of the relation of streptococci to Bright's disease — certainly a matter for lively discussion — which is dismissed with the bare statement (page 76) that "in the genito-urinary tract . . . streptococcus infection may occur such as cervicitis, orchitis, urethritis, cystitis and nephritis."

A few odd errors in the text, doubtless to be corrected in a subsequent edition, escaped the proofreader, such as "wholeproof" for "hole-proof" and "hyperurgy" for "hyperergy."

The Sex Technique in Marriage. By Isabel M. Hutton, M.D. Price, $2. Pp. 160. New York: Emerson Books, Inc., 1932.

This is the first American edition of a book which so far has appeared in three English editions and one Dutch. It made its first appearance in 1923, and was published by Heinemann.

The American edition is essentially the same as the ones previously published in England, and these already have been reviewed competently. *The Journal of the American Medical Association* (**82**:153 [Jan. 12] 1924) has described the first English edition as a practical work on the subject it discusses, written in plain, understandable language, and with good judgment as to what constitutes general medical opinion. This is a fair characterization of the current American edition. One might raise the question as to the necessity for a book of this character and agree with the *Medical Journal of Australia* that there is a limited sphere of usefulness for it; or one might reflect with the *British Medical Journal* as to how curious it is that civilization in man should have led to a necessity for instruction in such a natural instinctive act as consummation of marriage.

The book appears to suffer from an inferiority complex, which is unfortunate. It is too obviously self-conscious, and is published in this country by a firm hitherto unknown to libraries and booksellers; on the last few pages are reprinted many of the nice things that have been said of the earlier English editions by complimentary reviewers. This sort of self-advertising is likely to seem in bad taste to certain readers and is entirely unnecessary. Almost any one will admit that whatever demand there may be for a book containing this sort of instruction is well and honestly met by this volume. As President Lincoln is supposed to have said of a certain book, any one who likes this kind of book will find it just the kind of book they like.

Differential Diagnosis of Endocrine Disorders. By Allan W. Rowe, Director of Research, Evans Memorial, Massachusetts Memorial Hospital, Boston. Price, $4. Pp. 220, with 50 tables. Baltimore: Williams & Wilkins Company, 1932.

The material for this monograph was drawn from investigations in endocrinology which have been carried on at the Evans Memorial Laboratory since 1912, and summarizes observations made on a large group of people. The book is divided into three parts; these deal with a clinical consideration of the persons studied, with laboratory tests and with certain special examinations that have been completed.

Great emphasis is laid on the results of chemical tests as indicators of glandular function. The diagnosis of hypofunction, hyperactivity or dysfunction of any of the endocrine glands was accepted, however, only after exclusion of all known "non-endocrine" causes of variation from normal in the tests utilized. Some of the tests are not of much value to the internist, since their results may be affected so markedly by metabolic trends which are independent of internal secretions.

The tables include data yielding suggestive information in regard to the possible correlation of many different physical and chemical findings. To assemble these data, normal persons were compared with patients studied in a similar fashion but having endocrine disorders. A particularly valuable and interesting feature of the volume lies in the careful account it contains of the methods by which a complicated program of diagnostic studies can be completed without undue expenditure of time. These schedules should prove useful to clinics engaged in carrying on intensive research in endocrinology.

A Guide to Human Parasitology for Medical Students and Practitioners. By D. B. Blacklock and T. Southwell. Price, $4. Pp. 271. Baltimore: Williams & Wilkins Company, 1932.

The reviewer's first reaction to this guide to parasitology was "Well, why has this inevitable performance not been done before; why has relief not been brought sooner to the long-suffering general practitioner?" For this, in his opinion, is precisely what Blacklock and Southwell have done for those of us who, only occasionally seeing an instance of infestation with those fascinating "animals," have either regarded the subject as a terra incognita or at best have had a confused vision of crawling and creeping things attacking man, pig, cow, snail, fish and insect—a sort of a grand nature-fakery. Nor is the situation much relieved by turning to technical works on parasitology, for there one runs foul at the start of dentigerous ridges, gubernacula, cervical papillae and bursae copulatrices, not to mention plerocercoids and hexacanth embryos. In the present book all these difficulties are swept away and everything is made clear in a delightfully simple and yet thoroughly scholarly way; the matter becomes not only readable but almost romantic. Especially valuable aids to the nontechnical student are the admirably documented illustrations and charts and the tables in which the subject matter is classified from every possible point of view. Every medical student should have this compendium on his shelves.